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(54) Title: SARS VIRUS NUCLEOTIDE AND AMINO ACID SEQUENCES AND USES THEREOF

(57) Abstract: The invention provides, in part, the genomic sequence of a putative coronavirus, the SARS virus, and provides novel nucleic acid and amino acid sequences that may be used, for example, for the diagnosis, prophylaxis, or therapy of a variety of SARS virus related disorders.

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# SARS VIRUS NUCLEOTIDE AND AMINO ACID SEQUENCES AND USES THEREOF

#### Field of the Invention

The invention is in the field of virology. More specifically, the invention is in the field of coronaviruses.

### Background of the Invention

Severe acute respiratory syndrome (SARS), a worldwide outbreak of atypical pneumonia with an overall mortality rate of about 3 to 6%, has been attributed to a coronavirus following tests of causation according to Koch's postulates, including monkey inoculation (R. Munch, Microbes Infect 5, 69-74, Jan. 2003). The coronaviruses are members of a family of enveloped viruses that replicate in the cytoplasm of animal host cells (B. N. Fields et al., Fields virology, Lippincott Williams & Wilkins, Philadelphia, 4th ed., 2001). They are distinguished by the presence of a single-stranded plus sense RNA genome, approximately 30 kb in length, that has a 5' cap structure and 3' polyA tract. Hence the genome is essentially a very large mRNA. Upon infection of an appropriate host cell, the 5'-most open reading frame (ORF) of the viral genome is translated into a large polyprotein that is cleaved by viral-encoded proteases to release several nonstructural proteins including an RNA-dependent RNA polymerase (Pol) and an ATPase helicase (Hel). These proteins in turn are responsible for replicating the viral genome as well as generating nested transcripts that are used in the synthesis of the viral proteins. The mechanism by which these subgenomic mRNAs are made is not fully understood, however transcription regulating sequences (TRSs) at the 5'end of each gene may represent signals that regulate the discontinuous transcription of subgenomic mRNAs (sgmRNAs). The TRSs include a partially conserved core sequence (CS) that in some coronaviruses is 5'-CUAAAC-3'. Two major models have been proposed to explain the discontinuous transcription in coronaviruses and arterioviruses (M.M.C.Lai, D. Cavanagh, Adv Virus Res. 48,1(1997); S. G. Sawicki, D.L. Sawicki, Adv. Exp. Med Biol. 440,215(1998)). The

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discovery of transcriptionally active, subgenomic-size minus strands containing the antileader sequence and transcription intermediates active in the synthesis of mRNAs (D. L. Sawicki et al., J. Gen Virol 82,386 (2001); S. G. Sawicki, D.L. Sawicki, J. Virol. 64,1050 (1990); M. Schaad, R.S.J. Baric, J. Virol. 68,8169(1994); P. B. Sethna et al., Proc. Natl. Acad. Sci. U.S.A. 86,5626 (1989)) favors the model of discontinuous transcription during the minus strand synthesis (S. G. Sawicki, D.L. Sawicki, Adv. Exp. Med Biol. 440,215(1998)).

The coronaviral membrane proteins, including the major proteins S (Spike) and M (Membrane), are inserted into the endoplasmic reticulum Golgi intermediate compartment (ERGIC) while full length replicated RNA (+ strands) assemble with the N (nucleocapsid) protein. This RNA-protein complex then associates with the M protein embedded in the membranes of the ER and virus particles form as the nucleocapsid complex buds into the ER. The virus then migrates through the Golgi complex and eventually exits the cell, likely by exocytosis (B. N. Fields et al., Fields virology, Lippincott Williams & Wilkins, Philadelphia, 4<sup>th</sup> ed., 2001). The site of viral attachment to the host cell resides within the S protein.

The coronaviruses include a large number of viruses that infect different animal species. The predominant diseases associated with these viruses are respiratory and enteric infections, although hepatic and neurological diseases also occur with some viruses. Coronaviruses are divided into three serotypes, Types I, II and III. Phylogenetic analysis of coronavirus sequences also identifies three main classes of these viruses, corresponding to each of the three serotypes. Type II coronaviruses contain a hemagglutinin esterase (HE) gene homologous to that of Influenza C virus. It is presumed that the precursor of the Type II coronaviruses acquired HE as a result of a recombination event within a doubly infected host cell.

In view of the rapid worldwide dissemination of SARS, which has the potential of creating a pandemic, along with its alarming morbidity and mortality rates, it would be useful to have a better understanding of this coronavirus agent at the molecular level to provide diagnostics, vaccines, and therapeutics, and to support public health control measures.

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#### Summary of the Invention

In general, the invention provides the genomic sequence of a novel coronavirus, the SARS virus, and provides novel nucleic acid molecules encoding novel proteins that may be used, for example, for the diagnosis or therapy of a variety of SARS virus-related disorders.

In one aspect, the invention provides a substantially pure SARS virus nucleic acid molecule or fragment thereof, for example, a genomic RNA or DNA, cDNA, synthetic DNA, or mRNA molecule. In some embodiments, the nucleic acid molecule includes a sequence substantially identical to any of the sequences of SEQ ID NOs: 1-13, 15-18, 20-30, 90-159, 208, 209. In some embodiments, the nucleic acid molecule includes a sequence from SEQ ID NO: 1, SEQ ID NO:2, or SEQ ID NO: 15 or a fragment of these sequences. In alternative embodiments, the nucleic acid molecule may include a sequence substantially identical to SEQ ID NO: 1, SEQ ID NO: 2, or SEQ ID NO: 15, or a fragment thereof. In alternative embodiments, the nucleic acid molecule may include a s2m motif (for example, a s2m sequence substantially identical to any of the sequence of SEQ ID NOs: 16, 17, and 18), a leader sequence (for example, a sequence substantially identical to the sequence of SEQ ID NO: 3), or a transcriptional regulatory sequence (for example, a sequence substantially identical to any of the sequence of SEQ ID NOs: 4-13 and 20-30). In alternative embodiments, the nucleic acid molecule includes a sequence substantially identical to any of the sequences of nucleotides 265-13,398; 13,398-21,485; 21,492 - 25,259; 25,268 -26,092; 25,689 - 26,153; 26,117 - 26,347; 26,398 - 27,063; 27,074 - 27,265; 27,273 -27,641; 27,638 - 27,772; 27,779 - 27,898; 27,864 - 28,118; 28,120 - 29,388; 28,130 -28,426; 28,583 – 28,795; and 29,590 – 29,621 of SEQ ID NO: 15. In alternative embodiments, the nucleic acid molecule may encode a polyprotein or a polypeptide. In alternative embodiments, the invention provides a nucleic acid molecule including a sequence complementary to a SARS virus nucleotide sequence.

In an alternative aspect, the invention provides a substantially pure SARS virus polypeptide or fragment thereof, for example, a polyprotein, glycoprotein (for example, a matrix glycoprotein that may include a sequence substantially identical to the sequence of SEQ ID NO: 34), a transmembrane protein (for example, a multitransmembrane protein, a type I transmembrane protein, or a type II

transmembrane protein), a RNA binding protein, or a viral envelope protein. In alternative embodiments, the invention provides a replicase 1a protein, replicase 1b protein, a spike glycoprotein, a small envelope protein, a matrix glycoprotein, or a nucleocapsid protein. In alternative embodiments, the invention provides a nucleic acid molecule encoding a SARS virus polypeptide. In alternative embodiments, the SARS virus polypeptide includes an identifiable signal sequence (for example, a signal sequence substantially identical to the sequence of SEQ ID NOs: 76 or 85), a transmembrane domain (for example, a transmembrane domain substantially identical to any of the sequences of SEQ ID NOs: 77-86), a transmembrane anchor, a transmembrane helix, an ATP-binding domain, a nuclear localization signal, a hydrophilic domain, (for example, a hydrophilic domain substantially identical to the sequence of SEQ ID NOs: 87), or a lysine-rich sequence (for example, a sequence substantially identical to the sequence of SEQ ID NO: 14). In alternative embodiments, the SARS virus polypeptide may include a sequence substantially identical to any of the sequences of SEQ ID NOs: 14, 33-36, 64-74, and 76-87.

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In alternative embodiments, the invention provides a vector (for example, a gene therapy vector or a cloning vector) including a SARS virus nucleic acid molecule (for example, a molecule including a sequence substantially identical to any of the sequences of SEQ ID NOs: 1-13, 15-18, 20-30, 90-159, 208, 209), or a host cell (for example, a mammalian cell, a yeast, a bacterium, or a nematode cell) including the vector.

In alternative embodiments, the invention provides a nucleic acid molecule having substantial nucleotide sequence identity (for example, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% complementarity) to a sequence encoding a SARS virus polypeptide or fragment thereof, for example where the fragment includes at least six amino acids, and where the nucleic acid molecule hybridizes under high stringency conditions to at least a portion of a SARS virus nucleic acid molecule.

In alternative embodiments, the invention provides a nucleic acid molecule having substantial nucleotide sequence identity (for example, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% complementarity) to a SARS virus nucleotide sequence, for example where the nucleic acid molecule includes at least ten nucleotides, and where

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the nucleic acid molecule hybridizes under high stringency conditions to at least a portion of a SARS virus nucleic acid molecule.

In alternative embodiments, the invention provides a nucleic acid molecule comprising a sequence that is antisense to a SARS virus nucleic acid molecule, or an antibody (for example, a neutralizing antibody) that specifically binds to a SARS virus polypeptide.

In alternative embodiments, the invention provides a method for detecting a SARS epitope, such as a virion or polypeptide in a sample, by contacting the sample with an antibody that specifically binds a SARS epitope, such as a virus polypeptide, and determining whether the antibody specifically binds to the polypeptide. In alternative embodiments, the invention provides a method for detecting a SARS virus genome, gene, or homolog or fragment thereof in a sample by contacting a SARS virus nucleic acid molecule, for example where the nucleic acid molecule includes at least ten nucleotides, with a preparation of genomic DNA from the sample, under hybridization conditions providing detection of DNA sequences having nucleotide sequence identity to a SARS virus nucleic acid molecule. In alternative embodiments, the invention provides a method of targeting a protein for secretion from a cell, by attaching a signal sequence from a SARS virus polypeptide to the protein, such that the protein is secreted from the cell.

In alternative aspects, the invention provides a method for eliciting an immune response in an animal, by identifying an animal infected with or at risk for infection with a SARS virus and administering a SARS virus polypeptide or fragment thereof or fragment thereof, or administering a SARS virus nucleic acid molecule encoding a SARS virus polypeptide or fragment thereof to the animal. In alternative embodiments, the administering results in the production of an antibody in the mammal, or results in the generation of cytotoxic or helper T-lymphocytes in the mammal.

In alternative embodiments, the invention provides a kit for detecting the presence of a SARS virus nucleic acid molecule or polypeptide in a sample, where the kit includes a SARS virus nucleic acid molecule, or an antibody that specifically binds a SARS virus polypeptide.

In alternative aspects the invention provides a method for treating or preventing a SARS virus infection by identifying an animal (e.g., a human) infected with or at risk

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for infection with a SARS virus, and administering a SARS virus nucleic acid molecule or polypeptide, or administering a compound that inhibits pathogenicity or replication of a SARS virus, to the animal. In alternative embodiments, the invention provides the use of a SARS virus nucleic acid molecule or polypeptide for treating or preventing a SARS virus infection.

In alternative aspects the invention provides a method of identifying a compound for treating or preventing a SARS virus infection, by contacting sample including a SARS virus nucleic acid molecule or contacting a SARS virus polypeptide with the compound, where an increase or decrease in the expression or activity of the nucleic acid molecule or the polypeptide identifies a compound for treating or preventing a SARS virus infection.

In alternative aspects the invention provides a vaccine (e.g., a DNA vaccine) including a SARS virus nucleic acid molecule or polypeptide.

In alternative aspects the invention provides a microarray including a plurality of elements, wherein each element includes one or more distinct nucleic acid or amino acid sequences, and where the sequences are selected from a SARS virus nucleic acid molecule or polypeptide, or a antibody that specifically binds a SARS virus nucleic acid molecule or polypeptide.

In alternative aspects the invention provides a computer readable record (e.g., a database) including distinct SARS virus nucleic acid or amino acid sequences.

A "SARS virus" is a virus putatively belonging to the coronavirus family and identified as the causative agent for sudden acute respiratory syndrome (SARS). A SARS virus nucleic acid molecule may include a sequence substantially identical to the nucleotide sequences described herein or fragments thereof. A SARS virus polypeptide may include a sequence substantially identical to a sequence encoded by a SARS virus nucleic acid molecule, or may include a sequence substantially identical to the polypeptide sequences described herein, or fragments thereof.

A compound is "substantially pure" when it is separated from the components that naturally accompany it. Typically, a compound is substantially pure when it is at least 60%, more generally 75% or over 90%, by weight, of the total material in a sample. Thus, for example, a polypeptide that is chemically synthesized or produced by recombinant technology will be generally be substantially free from its naturally

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associated components. A nucleic acid molecule may be substantially pure when it is not immediately contiguous with (i.e., covalently linked to) the coding sequences with which it is normally contiguous in the naturally occurring genome of the organism from which the DNA of the invention is derived. A nucleic acid molecule may also be substantially pure when it is isolated from the organism in which it is normally found. A substantially pure compound can be obtained, for example, by extraction from a natural source; by expression of a recombinant nucleic acid molecule encoding a polypeptide compound; or by chemical synthesis. Purity can be measured using any appropriate method such as column chromatography, gel electrophoresis, HPLC, etc.

A "substantially identical" sequence is an amino acid or nucleotide sequence that differs from a reference sequence only by one or more conservative substitutions, as discussed herein, or by one or more non-conservative substitutions, deletions, or insertions located at positions of the sequence that do not destroy the biological function of the amino acid or nucleic acid molecule. Such a sequence can be at least 10%, 20%, 30%, 40%, 50%, 52.5%, 55% or 60% or 75%, or more generally at least 80%, 85%, 90%, or 95%, or as much as 99% or 100% identical at the amino acid or nucleotide level to the sequence used for comparison using, for example, the Align Program (Myers and Miller, CABIOS, 1989, 4:11-17) or FASTA. For polypeptides, the length of comparison sequences may be at least 4, 5, 10, or 15 amino acids, or at least 20, 25, or 30 amino acids. In alternate embodiments, the length of comparison sequences may be at least 35, 40, or 50 amino acids, or over 60, 80, or 100 amino acids. For nucleic acid molecules, the length of comparison sequences may be at least 15, 20, or 25 nucleotides, or at least 30, 40, or 50 nucleotides. In alternate embodiments, the length of comparison sequences may be at least 60, 70, 80, or 90 nucleotides, or over 100, 200, or 500 nucleotides. Sequence identity can be readily measured using publicly available sequence analysis software (e.g., Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wis. 53705, or BLAST software available from the National Library of Medicine, or as described herein). Examples of useful software include the programs Pile-up and PrettyBox. Such software matches similar sequences by assigning degrees of homology to various substitutions, deletions, insertions, and other modifications.

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Alternatively, or additionally, two nucleic acid sequences may be "substantially identical" if they hybridize under high stringency conditions. In some embodiments, high stringency conditions are, for example, conditions that allow hybridization comparable with the hybridization that occurs using a DNA probe of at least 500 nucleotides in length, in a buffer containing 0.5 M NaHPO<sub>4</sub>, pH 7.2, 7% SDS, 1 mM EDTA, and 1% BSA (fraction V), at a temperature of 65°C, or a buffer containing 48% formamide, 4.8x SSC, 0.2 M Tris-Cl, pH 7.6, 1x Denhardt's solution, 10% dextran sulfate, and 0.1% SDS, at a temperature of 42°C. (These are typical conditions for high stringency northern or Southern hybridizations.) Hybridizations may be carried out over a period of about 20 to 30 minutes, or about 2 to 6 hours, or about 10 to 15 hours, or over 24 hours or more. High stringency hybridization is also relied upon for the success of numerous techniques routinely performed by molecular biologists, such as high stringency PCR, DNA sequencing, single strand conformational polymorphism analysis, and in situ hybridization. In contrast to northern and Southern hybridizations, these techniques are usually performed with relatively short probes (e.g., usually about 16 nucleotides or longer for PCR or sequencing and about 40 nucleotides or longer for in situ hybridization). The high stringency conditions used in these techniques are well known to those skilled in the art of molecular biology, and examples of them can be found, for example, in Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, New York, N.Y., 1998, which is hereby incorporated by reference.

The terms "nucleic acid" or "nucleic acid molecule" encompass both RNA (plus and minus strands) and DNA, including cDNA, genomic DNA, and synthetic (e.g., chemically synthesized) DNA. The nucleic acid may be double-stranded or single-stranded. Where single-stranded, the nucleic acid may be the sense strand or the antisense strand. A nucleic acid molecule may be any chain of two or more covalently bonded nucleotides, including naturally occurring or non-naturally occurring nucleotides, or nucleotide analogs or derivatives. By "RNA" is meant a sequence of two or more covalently bonded, naturally occurring or modified ribonucleotides. One example of a modified RNA included within this term is phosphorothicate RNA. By "DNA" is meant a sequence of two or more covalently bonded, naturally occurring or modified deoxyribonucleotides. By "cDNA" is meant complementary or copy DNA produced from an RNA template by the action of RNA-dependent DNA polymerase

(reverse transcriptase). Thus a "cDNA clone" means a duplex DNA sequence complementary to an RNA molecule of interest, carried in a cloning vector.

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An "isolated nucleic acid" is a nucleic acid molecule that is free of the nucleic acid molecules that normally flank it in the genome or that is free of the organism in which it is normally found. Therefore, an "isolated" gene or nucleic acid molecule is in some cases intended to mean a gene or nucleic acid molecule which is not flanked by nucleic acid molecules which normally (in nature) flank the gene or nucleic acid molecule (such as in genomic sequences) and/or has been completely or partially purified from other transcribed sequences (as in a cDNA or RNA library). In some cases, an isolated nucleic acid molecule is intended to mean the genome of an organism such as a virus. An isolated nucleic acid of the invention may be substantially isolated with respect to the complex cellular milieu in which it naturally occurs. In some instances, the isolated material will form part of a composition (for example, a crude extract containing other substances), buffer system or reagent mix. In other circumstances, the material may be purified to essential homogeneity, for example as determined by PAGE or column chromatography such as HPLC. The term therefore includes, e.g., a genome; a recombinant nucleic acid incorporated into a vector, such as an autonomously replicating plasmid or virus; or into the genomic DNA of a prokaryote or eukaryote, or which exists as a separate molecule (e.g., a cDNA or a genomic DNA fragment produced by PCR or restriction endonuclease treatment) independent of other sequences. It also includes a recombinant nucleic acid which is part of a hybrid gene encoding additional polypeptide sequences. Preferably, an isolated nucleic acid comprises at least about 50, 80 or 90 percent (on a molar basis) of all macromolecular species present. Thus, an isolated gene or nucleic acid molecule can include a gene or nucleic acid molecule which is synthesized chemically or by recombinant means. Recombinant DNA contained in a vector are included in the definition of "isolated" as used herein. Also, isolated nucleic acid molecules include recombinant DNA molecules in heterologous host cells, as well as partially or substantially purified DNA molecules in solution. In vivo and in vitro RNA transcripts of the DNA molecules of the present invention are also encompassed by "isolated" nucleic acid molecules. Such isolated nucleic acid molecules are useful in the manufacture of the encoded polypeptide, as probes for isolating homologous sequences

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(e.g., from other species), for gene mapping (e.g., by in situ hybridization with chromosomes), or for detecting expression of the nucleic acid molecule in tissue (e.g., human tissue, such as peripheral blood), such as by Northern blot analysis.

Various genes and nucleic acid sequences of the invention may be recombinant sequences. The term "recombinant" means that something has been recombined, so that when made in reference to a nucleic acid construct the term refers to a molecule that is comprised of nucleic acid sequences that are joined together or produced by means of molecular biological techniques. The term "recombinant" when made in reference to a protein or a polypeptide refers to a protein or polypeptide molecule which is expressed using a recombinant nucleic acid construct created by means of molecular biological techniques. The term "recombinant" when made in reference to genetic composition refers to a gamete or progeny with new combinations of alleles that did not occur in the parental genomes. Recombinant nucleic acid constructs may include a nucleotide sequence which is ligated to, or is manipulated to become ligated to, a nucleic acid sequence to which it is not ligated in nature, or to which it is ligated at a different location in nature. Referring to a nucleic acid construct as "recombinant" therefore indicates that the nucleic acid molecule has been manipulated using genetic engineering, i.e. by human intervention. Recombinant nucleic acid constructs may for example be introduced into a host cell by transformation. Such recombinant nucleic acid constructs may include sequences derived from the same host cell species or from different host cell species, which have been isolated and reintroduced into cells of the host species. Recombinant nucleic acid construct sequences may become integrated into a host cell genome, either as a result of the original transformation of the host cells, or as the result of subsequent recombination and/or repair events.

As used herein, "heterologous" in reference to a nucleic acid or protein is a molecule that has been manipulated by human intervention so that it is located in a place other than the place in which it is naturally found. For example, a nucleic acid sequence from one species may be introduced into the genome of another species, or a nucleic acid sequence from one genomic locus may be moved to another genomic or extrachromasomal locus in the same species. A heterologous protein includes, for example, a protein expressed from a heterologous coding sequence or a protein

expressed from a recombinant gene in a cell that would not naturally express the protein.

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By "antisense," as used herein in reference to nucleic acids, is meant a nucleic acid sequence that is complementary to one strand of a nucleic acid molecule. In some embodiments, an antisense sequence is complementary to the coding strand of a gene, preferably, a SARS virus gene. The preferred antisense nucleic acid molecule is one which is capable of lowering the level of polypeptide encoded by the complementary gene when both are expressed in a cell. In some embodiments, the polypeptide level is lowered by at least 10%, or at least 25%, or at least 50%, as compared to the polypeptide level in a cell expressing only the gene, and not the complementary antisense nucleic acid molecule.

A "probe" or "primer" is a single-stranded DNA or RNA molecule of defined sequence that can base pair to a second DNA or RNA molecule that contains a complementary sequence (the target). The stability of the resulting hybrid molecule depends upon the extent of the base pairing that occurs, and is affected by parameters such as the degree of complementarity between the probe and target molecule, and the degree of stringency of the hybridization conditions. The degree of hybridization stringency is affected by parameters such as the temperature, salt concentration, and concentration of organic molecules, such as formamide, and is determined by methods that are known to those skilled in the art. Probes or primers specific for SARS virus nucleic acid sequences or molecules may vary in length from at least 8 nucleotides to over 500 nucleotides, including any value in between, depending on the purpose for which, and conditions under which, the probe or primer is used. For example, a probe or primer may be 8, 10, 15, 20, or 25 nucleotides in length, or may be at least 30, 40, 50, or 60 nucleotides in length, or may be over 100, 200, 500, or 1000 nucleotides in length. Probes or primers specific for SARS virus nucleic acid molecules may have greater than 20-30% sequence identity, or at least 55-75% sequence identity, or at least 75-85% sequence identity, or at least 85-99% sequence identity, or 100% sequence identity to the nucleic acid sequences described herein. In various embodiments of the invention, probes having the sequences: 5'- ATg AAT TAC CAA gTC AAT ggT TAC -3', SEQ ID NO: 160; 5'- gAA gCT ATT CgT CAC gTT Cg-3', SEQ ID NO: 161; 5'-CTg TAg AAA ATC CTA gCT ggA g-3', SEQ ID NO: 162; 5'- CAT AAC CAg TCg

SEQ ID NO: 180; 5'-

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gTA CAg CTA-3', SEQ ID NO: 163; 5'- TTA TCA CCC gCgAAg AAg CT-3', SEQ ID NO: 164; 5'- CTC TAg TTg CATgAC AgC CCT C-3', SEQ ID NO: 165; 5'- TCg TgC gTg gAT TggCTT TgA TgT-3', SEQ ID NO: 166; 5'-ggg TTg ggA CTA TCC TAA gTg TgA-3', SEQ ID NO: 167; 5'-TAA CAC ACA AAC ACC ATC ATC A-3', SEQ ID NO: 168; 5'-ggT Tgg gAC TAT CCT AAg TgT gA-3', SEQ ID NO: 169; 5'-CCA TCA TCA gAT AgA ATC ATC ATA-3', SEQ ID NO: 170; 5'- CCT CTC TTg TTC TTg CTC gCA-3', SEQ ID NO: 171; 5'- TAT AgT gAg CCg CCA CAC Atg-3', SEQ ID NO: 172; 5'-TAACACACACACACICCATCATCA-3', SEQ ID NO: 173; 5'-CTAACATGCTTAGGATAATGG-3', SEQ ID NO: 174; 5'-

10 GCCTCTCTTGTTCTTGCTCGC-3', SEQ ID NO: 175; 5'CAGGTAAGCGTAAAACTCATC-3', SEQ ID NO: 176; 5'TACACACCTCAGCGTTG-3', SEQ ID NO: 177; 5'-CACGAACGTGACGAAT-3',
SEQ ID NO: 178; 5'-GCCGGAGCTCTGCAGAATTC-3', SEQ ID NO: 179; 5'CAGGAAACAGCTATGAC TTGCATCACCACTAGTTGTGCCACCAGGTT-3',

TGTAAAACGACGGCCAGTTGATGGGATGGGACTATCCTAAGTGTGA-3', SEQ ID NO: 181; 5'- GCATAGGCAGTAGTTGCATC-3', SEQ ID NO: 182, as well as sequences amplified by specific combinations of these probes, may be excluded from specific uses according to the invention. Probes can be detectably-labeled, either radioactively or non-radioactively, by methods that are known to those skilled in the art. Probes can be used for methods involving nucleic acid hybridization, such as nucleic acid sequencing, nucleic acid amplification by the polymerase chain reaction, single stranded conformational polymorphism (SSCP) analysis, restriction fragment polymorphism (RFLP) analysis, Southern hybridization, northern hybridization, in situ hybridization, electrophoretic mobility shift assay (EMSA), and other methods that are known to those skilled in the art.

By "complementary" is meant that two nucleic acid molecules, e.g., DNA or RNA, contain a sufficient number of nucleotides that are capable of forming Watson-Crick base pairs to produce a region of double-strandedness between the two nucleic acids. Thus, adenine in one strand of DNA or RNA pairs with thymine in an opposing complementary DNA strand or with uracil in an opposing complementary RNA strand. It will be understood that each nucleotide in a nucleic acid molecule need not form a

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matched Watson-Crick base pair with a nucleotide in an opposing complementary strand to form a duplex.

By "vector" is meant a DNA molecule derived, e.g., from a plasmid, bacteriophage, or mammalian or insect virus, or artificial chromosome, that may be used to introduce a polypeptide, for example a SARS virus polypeptide, into a host cell by means of replication or expression of an operably linked heterologous nucleic acid molecule. By "operably linked" is meant that a nucleic acid molecule such as a gene and one or more regulatory sequences (e.g., promoters, ribosomal binding sites, terminators in prokaryotes; promoters, terminators, enhancers in eukaryotes; leader sequences, etc.) are connected in such a way as to permit the desired function e.g. gene expression when the appropriate molecules (e.g., transcriptional activator proteins) are bound to the regulatory sequences. A vector may contain one or more unique restriction sites and may be capable of autonomous replication in a defined host or vehicle organism such that the cloned sequence is reproducible. By "DNA expression vector" is meant any autonomous element capable of directing the synthesis of a recombinant peptide. Such DNA expression vectors include bacterial plasmids and phages and mammalian and insect plasmids and viruses. A "shuttle vector" is understood as meaning a vector which can be propagated in at least two different cell types, or organisms, for example vectors which are first propagated or replicated in prokaryotes in order for, for example, subsequent transfection into eukaryotic cells. A "replicon" is a unit that is capable of autonomous replication in a cell and may includes plasmids, chromosomes (e.g., mini-chromosomes), cosmids, viruses, etc. A replicon may be a vector.

A "host cell" is any cell, including a prokaryotic or eukaryotic cell, into which a replicon, such as a vector, has been introduced by for example transformation, transfection, or infection.

An "open reading frame" or "ORF" is a nucleic acid sequence that encodes a polypeptide. An ORF may include a coding sequence having i.e., a sequence that is capable of being transcribed into mRNA and/or translated into a protein when combined with the appropriate regulatory sequences. In general, a coding sequence includes a 5' translation start codon and a 3' translation stop codon.

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A "leader sequence" is a relatively short nucleotide sequence located at the 5' end of an RNA molecule that acts as a primer for transcription.

A "transcriptional regulatory sequence" "TRS" or "intergenic sequence" is a nucleotide sequence that lies upstream of an open reading frame (ORF) and serves as a template for the reassociation of a nascent RNA strand-polymerase complex.

A "frameshift mutation" is caused by a shift in a open reading frame, generally due to a deletion or addition of at least one nucleotide, such that an alternative polypeptide is ultimately translated.

By "detectably labeled" is meant any means for marking and identifying the presence of a molecule, e.g., an oligonucleotide probe or primer, a gene or fragment thereof, a cDNA molecule, a polypeptide, or an antibody. Methods for detectably-labeling a molecule are well known in the art and include, without limitation, radioactive labeling (e.g., with an isotope such as <sup>32</sup>P or <sup>35</sup>S) and nonradioactive labeling such as, enzymatic labeling (for example, using horseradish peroxidase or alkaline phosphatase), chemiluminescent labeling, fluorescent labeling (for example, using fluorescein), bioluminescent labeling, antibody detection of a ligand attached to the probe, or detection of double-stranded nucleic acid. Also included in this definition is a molecule that is detectably labeled by an indirect means, for example, a molecule that is bound with a first moiety (such as biotin) that is, in turn, bound to a second moiety that may be observed or assayed (such as fluorescein-labeled streptavidin). Labels also include digoxigenin, luciferases, and aequorin.

A "peptide," "protein," "polyprotein" or "polypeptide" is any chain of two or more amino acids, including naturally occurring or non-naturally occurring amino acids or amino acid analogues, regardless of post-translational modification (e.g., glycosylation or phosphorylation). An "polyprotein", "polypeptide", "peptide" or "protein" of the invention may include peptides or proteins that have abnormal linkages, cross links and end caps, non-peptidyl bonds or alternative modifying groups. Such modified peptides are also within the scope of the invention. The term "modifying group" is intended to include structures that are directly attached to the peptidic structure (e.g., by covalent coupling), as well as those that are indirectly attached to the peptidic structure (e.g., by a stable non-covalent association or by covalent coupling to additional amino acid residues, or mimetics, analogues or

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derivatives thereof, which may flank the core peptidic structure). For example, the modifying group can be coupled to the amino-terminus or carboxy-terminus of a peptidic structure, or to a peptidic or peptidomimetic region flanking the core domain. Alternatively, the modifying group can be coupled to a side chain of at least one amino acid residue of a peptidic structure, or to a peptidic or peptido-mimetic region flanking the core domain (e.g., through the epsilon amino group of a lysyl residue(s), through the carboxyl group of an aspartic acid residue(s) or a glutamic acid residue(s), through a hydroxy group of a tyrosyl residue(s), a serine residue(s) or a threonine residue(s) or other suitable reactive group on an amino acid side chain). Modifying groups covalently coupled to the peptidic structure can be attached by means and using methods well known in the art for linking chemical structures, including, for example, amide, alkylamino, carbamate or urea bonds.

A "polyprotein" is the polypeptide that is initially translated from the genome of a plus-stranded RNA virus, for example, a SARS virus. Accordingly, a polyprotein has not been subjected to post-translational processing by proteolytic cleavage into its processed protein products, and therefore, retains its cleavage sites. In some embodiments of the invention, the protease cleavage sites of a polyprotein may be modified, for example, by amino acid substitution, to result in a polyprotein that is incapable of being cleaved into its processed protein products.

An antibody "specifically binds" or "selectively binds" an antigen when it recognizes and binds the antigen, but does not substantially recognize and bind other molecules in a sample, having for example an affinity for the antigen which is 10, 100, 1000 or 10000 times greater than the affinity of the antibody for another reference molecule in a sample. A "neutralizing antibody" is an antibody that selectively interferes with any of the biological activities of a SARS virus polypeptide or polyprotein, for example, replication of the SARS virus, or infection of host cells. A neutralizing antibody may reduce the ability of a SARS virus polypeptide to carry out its specific biological activity by about 50%, or by about 70%, or by about 90% or more, or may completely abolish the ability of a SARS virus polypeptide to carry out its specific biological activity. Any standard assay for the biological activity of any SARS virus polypeptide, for example, assays determining expression levels, ability to infect host cells, or ability to replicate DNA, including those assays described herein or

known to those of skill in the art, may be used to assess potentially neutralizing antibodies that are specific for SARS virus polypeptides.

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A "signal sequence" is a sequence of amino acids that may be identified, for example by homology or biological activity to a peptide sequence with the known function of targeting a polypeptide to a particular region of the cell. Alsignal sequence or signal peptide may be a peptide of any length, that is capable of targeting a polypeptide to a particular region of the cell. In some embodiments, the signal sequence may direct the polypeptide to the cellular membrane so that the polypeptide may be secreted. In alternate embodiments, the signal sequence may direct the polypeptide to an intracellular compartment or organelle, such as the Golgi apparatus, or to the surface of a virus, such as the SARS virus. In alternate embodiments, a signal sequence may range from about 13 or 15 amino acids in length to about 60 amino acids in length.

A "transmembrane protein" is an amphipathic protein having a hydrophobic region ("transmembrane domain") that spans the lipid bilayer of the cell membrane from the cytoplasm to the cell surface, or spans the viral envelope, interspersed between hydrophilic regions on both sides of the membrane. The number of hydrophobic regions in an amphipathic protein is often proportional to the number of times that proteins spans the lipid bilayer. Thus, a single transmembrane protein spans the lipid bilayer once, and has a single transmembrane domain, while a multi-transmembrane protein spans the lipid bilayer multiple times. Multi-transmembrane proteins may enable virus entry into a host cell, or act to initiate transduction of a signal from the cell surface to the interior of the cell, for example, by a conformational change upon ligand binding. A "transmembrane anchor" is a transmembrane domain that maintains a polypeptide in its position in the cell membrane or viral envelope and is generally hydrophobic. A transmembrane anchor may generally be in the structure of an alpha helix, i.e., a "transmembrane helix". Multi-transmembrane proteins may have multiple transmembrane alpha-helices.

A "nuclear localization signal" is an amino acid sequence that permits the entry of a polypeptide into the nucleus of a cell through nuclear pores. A nuclear localization signal generally has a cluster of positively charged residues, for example, lysines. A "lysine-rich sequence" is a sequence having at least two contiguous lysine residues, or

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at least three contiguous lysine residues. In some embodiments, a lysine-rich sequence may be a nuclear localization signal.

An "ATP binding domain" is a consensus domain that is found in many ATP or GTP-binding proteins, and that forms a flexible loop (P-loop) between alpha-helical and beta pleated sheet domains. The general consensus for an ATP binding domain may be (A or G)-XXXXGK-(S or T).

A "RNA binding protein" is a protein that is capable of binding to a RNA molecule (see, for example, "RNA Binding Proteins: New Concepts in Gene Regulation" 1st ed, eds. K. Sandberg and S.E. Mulroney, Kluwers Academic Publishers, 2001). RNA binding proteins may contain common structural features such as arginine-rich tracts, for example, arginines alternating with aspartates, serines, or glycines, or zinc finger regions. RNA binding proteins may also have a common ribonucleotide sequence domain. RNA binding proteins are believed to play diverse roles in modulating post-transcriptional gene expression.

An "immune response" includes, but is not limited to, one or more of the following responses in a mammal: induction of antibodies, B cells, T cells (including helper T cells, suppressor T cells, cytotoxic T cells,  $\gamma\delta$  T cells) directed specifically to the antigen(s) in a composition or vaccine, following administration of the composition or vaccine. An immune response to a composition or vaccine thus generally includes the development in the host mammal of a cellular and/or antibody-mediated response to the composition or vaccine of interest. In general, the immune response will result in prevention or reduction of infection by a SARS virus.

An "immunogenic fragment" of a polypeptide or nucleic acid molecule refers to an amino acid or nucleotide sequence that elicits an immune response. Thus, an immunogenic fragment may include, without limitation, any portion of any of the SARS virus sequences described herein, or a sequence substantially identical thereto, that includes one or more epitopes (the antigenic determinant i.e., site recognized by a specific immune system cell, such as a T cell or a B cell). An "epitope" may include amino acids in a spatial orientation that they are non-contiguous in the amino acid sequence but are near each other due to the three dimensional conformation of the polypeptide. A epitope may include at least 3, 5, 8, or 10 or more amino acids. Immunogenic fragments or epitopes may be identified using standard methods known

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to those of skill in the art, such as epitope mapping techniques or antigenicity or hydropathy plots using, for example, the Omiga version 1.0 program from Oxford Molecular Group (see, for example, U. S. Patent No. 4,708,871). Immunogenic fragments or epitopes may also be identified using methods for determining three dimensional molecule structure such as X-ray crystallography or nuclear magnetic resonance.

A "sample" may be a tissue biopsy, amniotic fluid, cell, blood, serum, plasma, urine, stool, sputum, conjunctiva, or any other specimen, or any extract thereof, obtained from a patient (human or animal), test subject, or experimental animal. A "sample" may also be a cell or cell line created under experimental conditions, and constituents thereof (such as cell culture supernatants, cell fractions, infected cells, etc.). The sample may be analyzed to detect the presence of a SARS virus gene, genome, polypeptide, nucleic acid molecule or virion, or to detect a mutation in a SARS virus gene, expression levels of a SARS virus gene or polypeptide, or the biological function of a SARS virus polypeptide, using methods that are known in the art. For example, methods such as sequencing, single-strand conformational polymorphism (SSCP) analysis, or restriction fragment length polymorphism (RFLP) analysis of PCR products derived from a sample can be used to detect a mutation in a SARS virus gene; ELISA or western blotting can be used to measure levels of SARS virus polypeptide or antibody affinity; northern blotting can be used to measure SARS mRNA levels, or PCR can be used to measure the level of a SARS virus nucleic acid molecule.

Other features and advantages of the invention will be apparent from the following description of the drawings and the invention, and from the claims.

#### Brief Description of the Drawings

Figures 1A-D show phylogenetic analyses of SARS proteins. Unrooted phylogenetic trees were generated by clustalw (Thompson, J. D. et al., *Nucleic Acids Res* 22, 4673-80, Nov 11, 1994) bootstrap analysis using 1000 iterations. Genbank accessions for protein sequences are as follows: Figure 1A: Replicase 1A: BoCov (Bovine Coronavirus):AAL40396, 229E (Human Coronavirus):NP\_07355, MHV (Mouse Hepatitis Virus):NP\_045298, AIBV (Avian Infectious bronchitis

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virus):CAC39113, TGEV (Transmissible Gastroenteritis Virus): NP\_058423. Figure 1B: Matrix Glycoprotein: PHEV (Porcine hemagglutinating encephalomyelitis virus):AAL80035, BoCov (Bovine Coronavirus):NP\_150082, AIBV & AIBV2 (Avian infectious bronchitis virus): AAF35863 & AAK83027, MHV (Mouse hepatitis

- virus):AAF36439, TGEV (Transmissible gastroenteritis virus):NP\_058427, 229E & OC43 (Human Coronavirus): NP\_073555 & AAA45462, FCV (Feline coronavirus):BAC01160. Figure 1C: Nucleocapsid: MHV (Mouse hepatitis virus):P18446, BoCov (Bovine coronavirus):NP\_150083, AIBV (Avian infectious bronchitis virus):AAK27162, FCV (Feline coronavirus):CAA74230, PTGV (Porcine
- transmissible gastroenteritis virus): AAM97563, 229E & OC43 (Human coronavirus):NP\_073556 & P33469, PHEV (porcine hemagglutinating encephalomyelitis virus):AAL80036, TCV (Turkey coronavirus):AAF23873. Figure 1D: S (Spike) Protein: BoCov (Bovine coronavirus):AAL40400, MHV (Mouse hepatitis virus): P11225, OC43 & 229E (Human coronavirus):S44241 & AAK32191,
- PHEV (Porcine hemagglutinating encephalomyelitis virus):AAL80031, PRC (Porcine respiratory coronavirus):AAA46905, PEDV (Porcine epidemic diarrhea virus):CAA80971, CCov (Canine coronavirus):S41453, FICV (Feline infectious peritonitis virus):BAA06805, AIBV (Avian infectious bronchitis virus):AAO34396.

Figure 2 shows a schematic representation of the ORFs and s2m motif in the 20 29,736-base SARS virus genome.

Figures 3A-P show nucleotide sequences of the 29,736-base genome of the SARS virus (SEQ ID NOs: 1 and 2).

Figure 4 shows an alignment of the s2m regions from Avian infectious bronchitis virus (AIBV; SEQ ID NO: 32) and equine rhinovirus serotype 2 (ERV-2; SEQ ID NO: 31) with the 3' untranslated region (UTR; SEQ ID NO: 18) of the SARS virus (TOR2). The conserved areas in the s2m region are indicated by asterisks.

Figure 5 shows the amino acid sequence of the SARS virus S (Spike) Glycoprotein (SEQ ID NO: 33).

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Figure 6 shows the amino acid sequence of the SARS virus M (Matrix) Glycoprotein (SEQ ID NO: 34).

Figure 7 shows the amino acid sequence of the SARS virus E (Small envelope) protein (SEQ ID NO: 35).

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Figure 8 shows the amino acid sequence of the SARS virus N (Nucleocapsid) Protein (SEQ ID NO: 36).

Figure 9 shows an alignment of the matrix glycoprotein M from the SARS virus (Tor2\_M or ORF5; SEQ ID NO: 34) and various other matrix glycoproteins (SEQ ID NOs: 37-43). Asterisks (\*) indicate percentage identity to the SARS matrix protein as calculated by Align (Myers and Miller, CABIOS (1989) 4:11-17).

Figures 10A-B show an alignment of the nucleocapsid protein N from the SARS virus (Tor2\_N; SEQ ID NO: 36) and various other nucleocapsid proteins (SEQ ID NOs: 44-52). Asterisks (\*) indicate percentage identity to the SARS nucleocapsid protein calculated by Align (Myers and Miller, CABIOS (1989) 4:11-17) Figures 11A-K show the nucleotide sequence of the 29,751-base genome of the SARS virus (SEQ ID NO: 15).

Figure 12 shows a schematic representation of the ORFs and s2m motif in the 29,751-base SARS virus genome.

Figures 13A-D show phylogenetic analyses of SARS proteins. Unrooted 15 phylogenetic trees were generated by clustalw 1.74 (J. D. Thompson, D. G. Higgins, T. J. Gibson, Nucleic Acids Res 22, 4673-80 (Nov 11, 1994) using the BLOSUM comparison matrix and a bootstrap analysis of 1000 iterations. Numbers indicate bootstrap replicates supporting each node. Phylogenetic trees were drawn with the Phylip Drawtree program 3.6a3 (Felsenstein, J. 1993. PHYLIP (Phylogeny Inference 20 Package) version 3.5c. Distributed by the author. Department of Genetics, University of Washington, Seattle). Branch lengths indicate the number of substitutions per residue. Genbank accessions for protein sequences: A: Replicase 1A: BoCoV (Bovine Coronavirus): AAL40396, HCoV-229E (Human Coronavirus): NP 07355, MHV (Mouse Hepatitis Virus):NP\_045298, IBV (Avian Infectious bronchitis 25 virus):CAC39113, TGEV (Transmissible Gastroenteritis Virus): NP\_058423. B: Membrane Glycoprotein: PHEV (Porcine hemagglutinating encephalomyelitis virus): AAL80035, BoCoV (Bovine Coronavirus): NP 150082, IBV & IBV2 (Avian infectious bronchitis virus): AAF35863 & AAK83027, MHV (Mouse hepatitis virus): AAF36439, TGEV (Transmissible gastroenteritis virus): NP\_058427, HCoV-30 229E & HCoV-OC43 (Human Coronavirus): NP 073555 & AAA45462, FCoV (Feline coronavirus):BAC01160. C: Nucleocapsid: MHV (Mouse hepatitis virus):P18446,

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BoCoV (Bovine coronavirus):NP\_150083, IBV 1 & 2 (Avian infectious bronchitis virus): AAK27162 & NP\_040838, FCoV (Feline coronavirus):CAA74230, PTGV (Porcine transmissible gastroenteritis virus): AAM97563, HCoV-229E & HCoV-OC43 (Human coronavirus):NP\_073556 & P33469, PHEV (porcine hemagglutinating encephalomyelitis virus):AAL80036, TCV (Turkey coronavirus):AAF23873. D: S (Spike) Protein: BoCoV (Bovine coronavirus):AAL40400, MHV (Mouse hepatitis virus): P11225, HCoV-OC43 & HCoV-229E (Human coronavirus):S44241 & AAK32191, PHEV (Porcine hemagglutinating encephalomyelitis virus):AAL80031, PRCoV (Porcine respiratory coronavirus):AAA46905, PEDV (Porcine epidemic diarrhea virus):CAA80971, CCoV (Canine coronavirus):S41453, FIPV (Feline infectious peritonitis virus):BAA06805, IBV (Avian infectious bronchitis virus):AAO34396.

Figures 14A-F show an alignment of the spike glycoprotein S from the SARS virus (Tor2\_S; SEQ ID NO: 33) and various other spike glycoproteins (SEQ ID NOs: 53-62). Asterisks (\*) indicate percentage identity to the SARS spike protein as calculated by Align (Myers and Miller, CABIOS (1989) 4:11-17).

Figure 15 shows an alignment between the SARS virus Small envelope protein E (TOR2\_E; SEQ ID NO: 35) and the Envelope protein (Protein 4) (X1 protein) (ORF 3) from Porcine transmissible gastroenteritis coronavirus (strain Purdue). Swissprot accession number P09048 (PGV; SEQ ID NO: 63), as calculated by FASTA (http://www.ebi.ac.uk/fasta33/).

Figures 16A-B show the amino acid sequence of the SARS virus Replicase 1A protein (SEQ ID NO: 64).

Figure 17 shows the amino acid sequence of the SARS virus Replicase 1B protein (SEQ ID NO: 65).

Figure 18 shows the amino acid sequence of ORF3 of SARS virus (SEQ ID NO: 66).

Figure 19 shows the amino acid sequence of ORF4 of SARS virus (SEQ ID NO: 67).

Figure 20 shows the amino acid sequence (SEQ ID NO: 68) of ORF6 (nucleotides 27059-27247 of the 29,736-base genome sequence) or ORF 7 (nucleotides 27,074-27,265 of the 29,751-base genome sequence) of SARS virus.

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Figure 21 shows the amino acid sequence (SEQ ID NO: 69) of ORF7 (nucleotides 27258-27623 of the 29,736-base genome sequence) or ORF 8 (nucleotides 27,273-27,641 of the 29,751-base genome sequence), of SARS virus.

Figure 22 shows the amino acid sequence (SEQ ID NO: 70) of ORF8 (nucleotides 27623-27754 of the 29,736-base genome sequence) or ORF9 8 (nucleotides 27,638-27,772 of the 29,751-base genome sequence) of SARS virus.

Figure 23 shows the amino acid sequence (SEQ ID NO: 71) of ORF9 (nucleotides 27764-27880 of the 29,736-base genome sequence) or ORF10 (nucleotides 27,779-27,898 of the 29,751-base genome sequence) of SARS virus.

Figure 24 shows the amino acid sequence (SEQ ID NO: 72) of ORF10 (nucleotides 27849-28100 of the 29,736-base genome sequence) or ORF11 (nucleotides 27,864-28118 of the 29,751-base genome sequence) of SARS virus.

Figure 25 shows the amino acid sequence of ORF13 of SARS virus (SEQ ID NO: 73).

Figure 26 shows the amino acid sequence of ORF14 of SARS virus (SEQ ID NO: 74).

Figure 27 shows an alignment of the secreted region of the SARS virus ORF 10 of the 29,751-base genome sequence (sars) with the conotoxin from *Conus ventricosus* (conotoxin). Sequence identity is indicated by asterisks and sequence homology is indicated by dots.

#### Detailed Description of the Invention

In general, the invention provides nucleic acid molecules, polypeptides, and other reagents derived from a SARS virus, as well as methods of using such nucleic acid molecules, polypeptides, and other reagents.

The genome sequence (Figures 3A-P, 11A-K, SEQ ID NOs: 1, 2, and 15) reveals that the SARS coronavirus is only moderately related to other known coronaviruses, including two human coronaviruses, OC43 and 229E. Thus, the SARS virus is a previously unknown virus. The 5' end of the SARS genome contains a 5' leader sequence (Table 1; SEQ ID NO: 3) with sequence similarity to the highly conserved coronavirus core leader sequence, 5'-CUAAAC-3 (SEQ ID NO: 75;

Sawicki, S. G., et al., Adv Exp Med Biol 440, 215-9, 1998; Lai, M. M. and D. Cavanagh, Adv Virus Res 48, 1-100,1997). Transcriptional regulatory sequences (TRSs) were identified upstream of all open reading frames (ORFs) (Tables 1 and 2; SEQ ID NOs: 3-13 and 20-30). ORF9 and ORF10 of the 29,736-base SARS genome (ORF 10 and ORF 11 of the 29,751 base genome) overlap by 12 amino acids, and have matches to the TRS consensus in close proximity to their respective initiating methionine codons.

The 3' UTR sequence (SEQ ID NO: 18) of SARS virus contains a s2m region having the sequence ACATTTTCATCGAGGCCACGCGGAGTACGAT CGAGGGTACAGTGAAT; SEQ ID NO: 16) that includes a conserved, 10 discontinuous 32 base-pair s2m motif. The conserved 32 base-pair motif is a universal feature of astroviruses that has also been identified in avian coronavirus (AIBV) and the ERV-2 equine rhinovirus. This motif has been identified by Jonassen C.M. et al. (J Gen Virol 1998 Apr;79 (Pt 4):715-8) as GCCGNGGCCACGC(G/C) GAGTA(C/G)GANCGAGGGTACAG(G/C) (SEQ ID NO: 19), where N is generally 15 not part of the conserved motif, and can be any nucleotide. The region corresponding to the 32 base-pair motif in SARS virus includes the sequence: CGAGGCCACGCGGAGTACGATCGAGGGTACAG (SEQ ID NO: 17), and spans positions 29590-29621 of the 29,751 base genome. Figure 4 shows an alignment of the s2m regions from Avian infectious bronchitis virus (AIBV; SEQ ID NO: 32) and 20 equine rhinovirus serotype 2 (ERV-2; SEQ ID NO: 31), as defined in Jonassen C.M. et al. (J Gen Virol 1998 Apr; 79 (Pt 4):715-8), with the entire 3' untranslated region (UTR) of the SARS virus (TOR2) (SEQ ID NO: 18).

Table 1. Listing of the transcription regulatory sequences of the 29,736-base SARS genome, showing the nucleotide position (base) and associated open-reading frames (ORF). An asterisk (\*) indicates consensus sequence.

		· .					
5	Base	ORF	TRS Sequence	i			
	45	Leader	TCTCTAAACGAACTTTAAAATCTGTG	(SEQ	ID	NO:	3)
	21464	S	CAACTAAACGAACATG	(SEQ	ID	NO:	4)
	25238	ORF3	CACATAAACGAACTTATG	(SEQ	ID	NO:	5)
	26089	E	TGAGTACGAACTTATG	(SEQ	ID	NO:	6)
10	26326	M	GGTCTAAACGAACTAACT 40 ATG	(SEQ	ID	NO:	7)
	26986	ORF6	AACTATAAATT 62 ATG	(SEQ	ID	NO:	8)
	27244	ORF7	TCCATAAAACGAACATG	(SEQ	ID	NO:	9)
	27575	ORF8	TGCTCTAGTATTTTTAATACTTTG 24 ATG	(SEQ	ID	NO:	10)
	27751	ORF9	AGTCTAAACGAACATG	(SEQ	ID	NO:	11)
15	27837	ORF10	CTAATAAACCTCATG	(SEQ	ĪD	NO:	12)
	28084	N	TAAATAAACGAACAAATTAAAATG	(SEQ	ID	NO:	13)

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Table 2. Listing of the transcription regulatory sequences of the 29,751-base SARS genome, showing the nucleotide position (base), associated open-reading frames (ORF), and identified transcription regulatory sequences. Numbers in parentheses within the alignment indicate distance to the putative initiating codon. The conserved core sequence is indicated in bold in the putative leader sequence. Contiguous sequences identical to region of the leader sequence containing the core sequence are shaded. No putative TRSs were detected for ORFs 4, 13 and 14, although ORF 13 may share the TRS associated with the N protein.

	Base	ORF	TRS Sequence	
10	60	Leader	UCUCUAAACGAACUUUAAAAUCUGUG(SEQ ID NO: 20)	
	21479	S(Spike)	CAACUAAACGAACAUG (SEQ ID NO: 21)	
	25252	ORF3	CACAUAAACGAACUUAUG (SEQ ID NO: 22)	
	26104	Envelope	UGAGUACGAACUUAUG (SEQ ID NO: 23)	
,	26341	M	GGUCUAAACGAAGUAACU (40)AUG(SEQ ID NO:24)	
15	27001	ORF7	AAÇUANAAAUU (62)AUG(SEQ ID NO:25)	
	27259	ORF8	UCCAUAAAACGAACAUG (SEQ ID NO: 26)	
	27590	ORF9	UGCUCUAGUAUUUUUAAUACUUUG(24)AUG(SEQ ID 1	NO:27)
	27766	ORF10	AGUCUĀAAČGĀĀCAUG (SEQ ID NO: 28)	,
	27852	ORF11	CUAAUAÄACCUCAUG (SEQ ID NO: 29)	
20	28099	NUCLEOCAPSID	uaaauaaacgaacaaauuaaaaug (seq id no: 30)	

The coding potentials of the 29,736-base and 29,751-base genomes are depicted in Figures 2 and 12, respectively. Open reading frames (ORFs) include the Replicase 1a and 1b translation products, the Spike glycoprotein, the small Envelope protein, the Membrane and the Nucleocapsid protein. Construction of unrooted phylogenetic trees using this set of known proteins from representatives of the three known coronaviral groups reveals that the proteins encoded by the SARS virus do not readily cluster more closely with any known group than with any other (Figures 1A-D and 13A-D). In addition, nine novel ORFs have been analyzed.

The Replicase 1a ORF located at nucleotides 250-13395 of the 29,736-base genome, and nucleotides 265-13,398 of the 29,751-base genome, and replicase 1b ORF located at nucleotides 13395-21467 of the 29,736-base genome, and nucleotides 13,398 - 21,485 of the 29,751-base genome, occupy 21.2 kb of the SARS virus genome (Figures 2 and 12). These genes encode a number of proteins that are produced by proteolytic cleavage of a large polyprotein (Ziebuhr, J. et al., *J Gen Virol* 81, 853-79,

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Apr, 2000). A frame shift mutation interrupts the protein-coding region, separating the 1a and 1b open-reading frames. The proteins encoded by the Replicase 1a and 1b ORFs are depicted in Figures 16A-B and 17, SEQ ID NOs: 64 and 65).

The Spike glycoprotein (S) (E2 glycoprotein gene; Figures 2 and 12; nucleotides 21477 to 25241 of the 29,736-base genome, and nucleotides 21.492 to 25,259 of the 29,751-base genome) encodes a surface projection glycoprotein precursor of about 1,255 amino acids in length (Figure 5; SEQ ID NO: 33), which may be significant in the virulence of the SARS virus. Mutations in this gene are correlated with altered pathogenesis and virulence in other coronaviruses (B. N. Fields et al., Fields virology (Lippincott Williams & Wilkins, Philadelphia, ed. 4th, 2001). In other coronaviruses, the mature spike protein is inserted in the viral envelope with the majority of the protein exposed on the surface of the particles. Three molecules of the Spike protein form the characteristic peplomers or corona-like structures of this virus family. Analysis of the spike glycoprotein with SignalP (Nielson, H. et al., Prot Engineer. 10:1-6 (1997) indicates a signal peptide (MFIFLLFLTLTSG; SEQ ID NO: 76)(probability 0.996) with cleavage between residues 13 and 14. TMHMM (Sonnhammer, E. L. et al., Proc Int Conf Intell Syst Mol Biol 6, 175-82 (1998)) indicates a transmembrane domain near the C-terminal end (WYVWLGFIAGLIAIVMVTILLCC; SEQ ID NO: 183). Together these data indicate a type I membrane protein with N-terminus and the majority of the protein (residues 14-1195) on the outside of the cell-surface or virus particle, which may be responsible for binding to a cellular receptor. The SARS virus Spike glycoprotein has limited sequence identity to other, known Spike glycoproteins (Figures 14A-F).

ORF 3 (Figures 2 and 12; nucleotides 25253-26074 of the 29,736-base genome and nucleotides 25,268 - 26,092 of the 29,751-base genome) encodes a protein of 274 amino acids (Figure 18; SEQ ID NO: 66) that lacks significant similarities to any known protein when analyzed with BLAST (Altschul, S. F. et al., *Nucleic Acids Res* 25, 3389-402, Sep 1, 1997), FASTA (Pearson, W. R. and D. J. Lipman, *Proc Natl Acad Sci USA* 85, 2444-8, Apr, 1988) or PFAM (Bateman, A. et al., *Nucleic Acids Res* 30, 276-80, Jan 1, 2002). Analysis of the N-terminal 70 amino acids with SignalP indicates the existence of a signal peptide (MDLFMRFFTLRSITAQ; SEQ ID NO: 184) and a cleavage site (probability 0.540). Both TMpred (Hofman, K. and W. Stoffel, *Biol*.

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Chem. Hoope-Seyler 374, 166 (1993) and TMHMM indicate three trans-membrane regions spanning approximately residues 34-56 (TIPLQASLPFGWLVIGVAFLAVF, SEQ ID NO: 77), 77-99 (FQFICNLLLLFVTIYSHLLLVAA, SEQ ID NO: 78), and 103-125 (AQFLYLYALIYFLQCINACRIIM, SEQ ID NO: 79). Both TMpred and TMHMM indicate that the C-terminus and a large 149 amino acid domain is located inside the viral or cellular membrane. The C-terminal (interior) region of the protein, corresponding to about amino acids 124-274

(MRCWLCWKCKSKNPLLYDANYFVCWHTHNYDYCIPYNSVTDTIVVTEGDGI STPKLKEDYQIGGYSEDRHSGVKDYVVVHGYFTEVYYQLESTQITTDTGIENAT FFIFNKLVKDPPNVQIHTIDGSSGVANPAMDPIYDEPTTTTSVPL; SEQ ID NO: 185) may encode a protein domain with ATP-binding properties (PD037277).

ORF 4 (Figure 12; nucleotides 25,689 - 26,153 of the 29,751-base genome) encodes a predicted protein of 154 amino acids (Figure 19; SEQ ID NO: 67). This ORF overlaps entirely with ORF 3 and the E protein. ORF4 may be expressed from the ORF mRNA using an internal ribosomal entry site. BLAST analyses failed to identify matching sequences. Analysis with TMPred predicts a single transmembrane helix, amino acids 1-20 MMPTTLFAGTHITMTTVYHI, SEQ ID NO: 186.

The small envelope protein E (Figures 2 and 12; nucleotides 26102-26329 of the 29,736-base genome and nucleotides 26,117 - 26,347, ORF 5, of the 29,751genome) encodes a protein of 76 amino acids (Figure 7; SEQ ID NO: 35). BLAST and 20 FASTA comparisons indicate that the protein, while novel, is homologous to multiple envelope proteins (alternatively known as small membrane proteins) from several coronaviruses. An alignment of the SARS virus E protein with the envelope protein of Porcine transmissible gastroenteritis coronavirus indicates approximately 28% sequence identity between the two proteins over a 61 amino acid overlap, as calculated 25 by FASTA (Figure 15). PFAM analysis of the protein indicates that the small envelope protein E is a member of the NS3\_EnvE protein family. InterProScan (R. Apweiler et al., Nucleic Acids Res 29, 37-40, Jan 1, 2001; Zdobnov, E. M. and R. Apweiler, Bioinformatics 17, 847-8, Sep, 2001) analysis indicates that the protein is a component of the viral envelope, and homologs of it are found in other viruses, including 30 gastroenteritis virus and murine hepatitis virus. SignalP analysis indicates the presence of a transmembrane anchor (probability 0.939). TMpred analysis indicates a similar

transmembrane anchor at positions 17-34 (VLLFLAFVVFLLVTLAIL, SEQ ID NO: 80), which is consistent with the known association of homologous proteins with the viral envelope. TMHMM indicates a type II membrane protein with the majority of the 46 residue C terminus hydrophilic domain (

TALRLCAYCCNIVNVSLVKPTVYVYSRVKNLNSSEGVPDLLV; SEQ ID NO: 187) located on the surface of the viral particle. The E protein may be important for viral replication.

The Matrix glycoprotein M (Figures 2 and 12; nucleotides 26383-27045 of the 29,736-base genome and nucleotides 26,398 - 27,063, ORF 6, of the 29,751-genome) encodes a protein of 221 amino acids (Figure 6; SEQ ID NO: 34). BLAST and FASTA 10 analysis of the protein, while novel, reveals homologies to coronaviral matrix glycoproteins (Figure 9). The association of the spike glycoprotein (S) with the matrix glycoprotein (M) may be an essential step in the formation of the viral envelope and in the accumulation of both proteins at the site of virus assembly. Analysis of the amino acid sequence with SignalP indicates a signal sequence (probability 0.932), located at 15 approximately residues 1-39 (MADNGTITVEELKQLLEQWNLVIGFLFLAWIMLLQFAYS; SEQ ID NO: 188) that is unlikely to be cleaved. TMHMM and TMpred analysis both indicate the presence of three trans-membrane helices, located at approximately residues 15-37 20 (LLEOWNLVIGFLFLAWIMLLQFA; SEQ ID NO: 81), 50-72 (LVFLWLLWPVTLACFVLAAVYRI; SEQ ID NO: 82) and 77-99 (GGIAIAMACIVGLMWLSYFVASF; SEQ ID NO: 83), with the 121 amino acid hydrophilic domain on the inside of the virus particle, where it may interact with nucleocapsid. The hydrophilic domain may run from approximately amino acids PLRGTIVTRPLMESELVIGAVIIRGHLRMAGHSLGRCDIKDLPKEITVATSRTLS 25 YYKLGASQRVGTDSGFAAYNRYRIGNYKLNTDHAGSNDNIALLVQ (SEQ ID NO: 189) i.e. approximately amino acids 95 or 99 to 221 of SEQ ID NO: 34. PFAM analysis reveals a match to PFAM domain PF01635, and alignments to 85 other sequences in the PFAM database bearing this domain, which is indicative of the 30 coronavirus matrix glycoprotein.

ORF6 (Figure 2; nucleotides 27059-27247 of the 29,736-base genome sequence) or ORF 7 (Figure 12; nucleotides 27,074-27,265 of the 29,751-base genome

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sequence) encodes a protein of 63 amino acids (Figure 20; SEQ ID NO: 68). TMpred analysis indicates a trans-membrane helix located between residues 3 or 4 and 22 (HLVDFQVTIAEILIIIMRTF; SEQ ID NO: 84), with the N-terminus located outside the viral particle.

Similarly, the gene encoding ORF7 (Figure 2; nucleotides 27258-27623 of the 29,736-base genome sequence) or ORF 8 (Figure 12; nucleotides 27,273-27,641 of the 29,751-base genome sequence), encoding a protein of 122 amino acids (Figure 21; SEQ ID NO: 69), has no significant BLAST or FASTA matches to known proteins.

Analysis of this sequence with SignalP indicates a cleaved signal sequence (MKIILFLTLIVFTSC; SEQ ID NO: 85) (probability 0.995), with the cleavage site located between residues 15 and 16. TMpred and TMHMM analysis also indicates a trans-membrane helix located approximately at residues 99-117 (SPLFLIVAALVFLILCFTI; SEQ ID NO: 86). Together these data indicate that this protein is a type I membrane protein with the major hydrophilic domain of the protein (residues 16-98; ELYHYQECVRGTTVLLKEPCP SGTYEGNSPFHPLADNKFALTCTSTHFAFACADGTRHTYQLRARSVSPKLFIRQ EEVQQELY; SEQ ID NO: 87) and the amino-terminus is oriented inside the lumen of the ER/Golgi, or on the surface of the cell membrane or virus particle, depending on the membrane localization of the protein.

ORF8 (Figure 2; nucleotides 27623-27754 of the 29,736-base genome sequence) or ORF9 (Figure 12; nucleotides 27,638-27,772 of the 29,751-base genome sequence), encodes a protein of 44 amino acids (Figure 22; SEQ ID NO: 70). FASTA analysis of this sequence revealed some weak similarities (37% identity over a 35 amino acid overlap) to Swiss-Prot accession Q9M883, annotated as a putative sterol-C5 desaturase. A similarly weak match to a hypothetical *Clostridium perfringens* protein (Swiss-Prot accession CPE2366) was also detected. TMpred indicated a single strong trans-membrane helix FYLCFLAFLLFLVLIMLIIFWFS, SEQ ID NO: 190, with little preference for alternate models in which the N-terminus was located inside or outside the particle.

Similarly ORF9 (Figure 2; nucleotides 27764-27880 of the 29,736-base genome sequence) or ORF10 (Figure 12; nucleotides 27,779-27,898 of the 29,751-base genome sequence) encoding a protein of 39 amino acids (Figure 23; SEQ ID NO: 71), exhibited

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no significant matches in BLAST and FASTA searches but encodes a trans-membrane helix LLIVLTCISLCSCICTVVQ (SEQ ID NO: 191) by TMPred, with the N-terminus located within the viral particle. The region immediately upstream of this protein exhibits a strong match to the TRS consensus (Table 2), indicating that a transcript initiates from this site. The large number of cysteine residues (6) may result in cross linking of the amino acids. Amino acids ICTVVQRCASNKPHVLEDPCKVQH (SEQ ID NO: 192) of this protein may be secreted. The secreted amino acids exhibit homology to toxin proteins, for example, to the conotoxin of *Conus ventricosus* (Figure 27). Antigenic peptides from the hydrophilic (secreted) region, for example, CICTVVQRCASNKPHVLEDPCK (SEQ ID NO: 193), were used to generate monoclonal antibodies using standard techniques. Furthermore, the C terminal amino acids form a sequence that shares homology to farnesylation sites (CKQH), which generally require C terminal location to be functional. This protein may act as a virulence factor and/or may facilitate transmission to humans.

ORF10 (Figure 2; nucleotides 27849-28100 of the 29,736-base genome sequence) or ORF11 (Figure 12; nucleotides 27,864-28118 of the 29,751-base genome sequence) encoding a protein of 84 amino acids (Figure 24; SEQ ID NO: 72) exhibited only very short (9-10 residues) matches to a region of the human coronavirus E2 glycoprotein precursor (starting at residue 801). Analysis by SignalP and TMHMM predict a soluble protein. A detectable alignment to the TRS consensus sequence was also found (Table 2).

The protein (422 amino acids; Figure 8; SEQ ID NO: 36) encoded by the Nucleocapsid gene (Figure 2; nucleotides 28105-29370 of the 29,736-base genome sequence; Figure 12, nucleotides 28,120-29,388 of the 29,751-base genome sequence) aligns well with nucleocapsid proteins from other representative coronaviruses (Figures 10A-B), although a short lysine rich region (KTFPPTEPKKDKKKKTDEAQ; SEQ ID NO: 14) is unique to SARS. This region is suggestive of a nuclear localization signal Since some coronaviruses are able to replicate in enucleated cells, the SARS virus nucleocapsid protein may have evolved a novel nuclear function, which may play a role in pathogenesis. In addition, the basic nature of this peptide suggests it may assist in RNA binding. The SARS nucleocapsid protein is also a good candidate for diagnostic tests.

ORF 13 (Fig. 12; nucleotides 28,130 – 28,426 of the 29,751-base genome sequence) encodes a novel protein of 98 amino acids (Figure 25; SEQ ID NO: 73). ORF 14 (Fig. 12; nucleotides 28,583 – 28,795 of the 29,751-base genome sequence) encodes a novel protein of 70 amino acids (Figure 26; SEQ ID NO: 74). TMPred predicts a single transmembrane helix VVAVIQEIQLLAAVGEILLLEW (SEQ ID NO: 194).

Various features of the SARS virus genome are summarised in Table 3. While Table 3 refers to the 29,751-base genome sequence, the features are also applicable to the 29,736-base genome sequence (SEQ ID NOs: 1 and 2).

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Table 3. Features of the SARS virus 29,751-base genome sequence.

Feature	Start - End1	No. amino acids	No. bases	Frame	TRS
Orf 1a	265 - 13,398	4,382	13,149	+1	N/A
Orf 1b	13,398 – 21,485	2,628	7,887	+3	N/A
S protein	21,492 – 25,259	1,255	3,768	+3	Strong
Orf 3	25,268 – 26,092	274	825	+2	Strong
Orf 4	25,689 – 26,153	154	465	+3	Absent <sup>2</sup>
E protein	26,117 – 26,347	76	231	+2	Weak
M protein	26,398 – 27,063	221	666	+1	Strong
Orf 7	27,074 – 27,265	63	192	+2	Weak
Orf 8	27,273 – 27,641	122	369	+3	Strong
Orf 9	27,638 – 27,772	44	135	+2	Weak
Orf 10	27,779 – 27,898	39	120	+2	Strong
Orf 11	27,864 - 28,118	84	255	+3	Weak
N protein	28,120 – 29,388	422	1,269	+1	Strong
Orf 13 <sup>3</sup>	28,130 - 28,426	98	297	+2	Absent <sup>2</sup>
Orf 14 <sup>3</sup>	28,583 – 28,795	70	213	+2	Absent
s2m motif	29,590 - 29,621	N/A	30	N/A	N/A

<sup>1.</sup> End coordinates include the stop codon, except for ORF 1a and s2m.

Various polymorphisms may exist in the SARS virus. In the SARS 29,736-base genome sequences (SEQ ID NO: 1 or 2), for example, nucleotides 7904, 16607, 19168,

<sup>2</sup> These ORFs overlap substantially or completely with other and may share TRSs.

<sup>15</sup> N/A indicates not applicable.

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24857, or 26842 may be C or T; or nucleotides 19049, 23205, or 25283 may be G or A, and in the SARS 29,751-base genome sequence (SEQ ID NO: 15), for example, nucleotides 7919, 16622, 19183, 24872, or 26857 may be C or T; or nucleotides 19064, 23220, or 25298 may be G or A. In some embodiments, the nucleotide changes may result in no change in the encoded amino acid, or in a conservative or non-conservative change in the encoded amino acid. In some embodiments, a nucleotide change, as described herein, at position 7904 or 7919, may result in a A to V amino acid substitution, in the Replicase 1A protein coding region; a change at position 19168 or 19183 may result in a V to A amino acid substitution, in the Replicase IB protein coding region; a change at position 23205 or 23220 may result in a A to S amino acid substitution (non-conservative change), affecting the Spike glycoprotein coding region; a change at position 25283 or 25298 may result in a R to G amino acid substitution (non-conservative change), affecting ORF3; or a change at position 26842 or 26857 may result in a S to P amino acid substitution (non-conservative change), affecting the Nucleocapsid protein coding region, in the SARS 29,736-base (SEQ ID NO: 1 or 2) and 29.751-base genome (SEQ ID NO: 15) sequences, respectively. In various embodiments, a nucleotide or amino acid sequence including a particular polymorphism may be selected, for example, for use in the methods of the invention, or may be excluded, for example, from a particular use according to the invention.

Various alternative embodiments of the invention are described below. These embodiments include, without limitation, identification and use of SARS virus nucleic acid and amino acid sequences for diagnostic or therapeutic uses.

#### Diagnosis of SARS virus-related disorders

A SARS virus-related disorder is any disorder that is mediated by the SARS virus, or by a nucleic acid molecule or polypeptide derived from the SARS virus. Accordingly, SARS virus nucleic acid molecules and polypeptides may be used to diagnose and identify a SARS virus-related disorder in a mammal, for example, a human or a domestic, farm, wild, or experimental animal. In some embodiments, SARS virus nucleic acid molecules and polypeptides may be used to screen such animals, e.g., civet cats, for the presence of SARS virus. A SARS virus-related disorder may be a hepatic, enteric, respiratory, or neurological disorder, and may be

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accompanied by one or more symptoms or indications including, but not limited to, fever, cough, shortness of breath, headache, low blood oxygen concentration, liver damage, or reduced lymphocyte numbers. Accordingly, samples for diagnosis may be obtained from cells, blood, serum, plasma, urine, stool, conjunctiva, sputum, asopharyngeal or oropharyngeal swabs, tracheal aspirates, bronchalveolar lavage, pleural fluid, amniotic fluid, or any other specimen, or any extract thereof, or by tissue biopsy of for example lungs or major organs, obtained from a patient (human or animal), test subject, or experimental animal.

A SARS virus-related disorder may be diagnosed by amplifying a SARS nucleic acid molecule or fragment thereof from a sample. Probes or primers for use in amplification may be prepared using standard techniques. In some embodiments, probes or primers are selected from regions of a SARS virus genome as described herein that show limited sequence homology or identity (e.g., less than 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% identity) to other viruses or pathogens, or to host sequences.

Nucleic acid sequences can be amplified as needed by methods known in the art. For example, this can be accomplished by e.g., polymerase chain reaction "PCR" of DNA or of RNA by reverse transcriptase-PCR or "RT-PCR" (See generally PCR Technology: Principles and Applications for DNA Amplification (ed. H. A. Erlich, Freeman Press, NY, N.Y., 1992); PCR Protocols: A Guide to Methods and Applications (eds. Innis, et al., Academic Press, San Diego, Calif., 1990); Mattila et al., Nucleic Acids Res. 19, 4967 (1991); Eckert et al., PCR Methods and Applications 1, 17 (1991); PCR (eds. McPherson et al., IRL Press, Oxford); and U.S. Pat. No. 4,683,202 issued July 28, 1987 to Mullis) Variations of standard PCR techniques, such as for example real time RT-PCR using internal as well as amplification primers, resulting in increased sensitivity and speed, and reduction of risk of sample contamination (see for example Higuchi, R., et al., "Kinetic PCR Analysis: Real-time Monitoring of DNA Amplification Reactions," Bio/Technology, vol. 11, pp. 1026-1030 (1993); Heid et al, "Real Time Quantitative PCT", Genome Research, 1996, pp. 986-994; Gibson UE et al., "A novel method for real time quantitative RT-PCR," Genome Res. 1996 Oct:6(10):995-1001), or the "Tacman" approach to PCR, described by for example Holland et al, Proc. Natl. Acad. Sci., 88: 7276-7280 (1991), may be performed.

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Other suitable amplification and analytical methods include the single base primer extension (see for example U.S. Patent No. 6,004,744), mini-sequencing, ligase chain reaction (LCR) (see for example Wu and Wallace, Genomics 4, 560 (1989), Landegren et al., Science 241, 1077 (1988), transcription amplification (Kwoh et al., Proc. Natl. Acad. Sci. USA 86, 1173 (1989)), and self-sustained sequence replication (Guatelli et al., Proc. Nat. Acad. Sci. USA, 87, 1874 (1990)) and nucleic acid based sequence amplification (NASBA). The latter two amplification methods involve isothermal reactions based on isothermal transcription, which produce both single stranded RNA (ssRNA) and double stranded DNA (dsDNA) as the amplification products in a ratio of about 30 or 100 to 1, respectively.

A SARS virus-related disorder may also be diagnosed using an antibody directed against a SARS virus nucleic acid or amino acid sequence that specifically binds a nucleic acid molecule or polypeptide. In an alternative embodiment, the antibody may be directed against a SARS polypeptide, for example, the S polypeptide or fragment thereof that is located on the surface of the SARS virion. Methods for preparation of antibodies or for assaying antibody binding are well known in the art.

Serological diagnosis may included detection of antibodies against a SARS virus polypeptide or nucleic acid molecule, e.g., the Nucleocapsid protein, produced in response to infection using techniques such as indirect fluorescent antibody testing or enzyme-linked immunosorbent assays (ELISA). A SARS virus-related disorder may also be diagnosed by for example performing *in situ* probe hybridization studies on tissue specimens.

In some aspects, diagnostic tests as described herein or known to those of skill in the art may be performed for SARS virus variants that exhibit increased pathogenicity, such as strains having redundant sequences.

In some embodiments, reagents for diagnosis (e.g., probes, primers, antibodies, etc.) may be provided in kits which may optionally include instructions for using the reagent or may include other reagents for performing the appropriate assay e.g., controls, standards, buffers, etc.

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Compounds according to the invention may also be used to provide therapeutics or prophylactics for SARS virus-related disorders. Accordingly, such compounds may be used to treat a mammal, for example, a human or a domestic, farm, wild, or experimental animal that has or is at risk for a SARS virus-related disorder. Such compounds may include, without limitation, compounds that interfere with SARS virus replication, expression of SARS virus proteins, or the ability of the SARS virus to infect a host cell. Accordingly, in some embodiments, compounds that act as antagonists to SARS virus polypeptides may be used as therapeutics or prophylactics for SARS virus related disorders. In some embodiments, purified SARS virus polypeptides may be used as for example competitive inhibitors to disrupt viral function. For example, a Spike protein lacking a functional domain, or having some other modification that maintains binding but reduces or eliminates pathogenicity, may be used to disrupt viral function. In some embodiments, antibodies that bind SARS virus polypeptides or nucleic acid molecules, for example, humanized antibodies, may be used as therapeutics or prophylactics.

In some embodiments, the SARS-virus compounds may be used as vaccines, or may be used to develop vaccines. For example, peptides derived from portions of SARS-virus proteins or polypeptides located on the outside of the virion or cell surface may be useful for vaccines or for generation of therapeutic or prophylactic antibodies.

A "vaccine" is a composition that includes materials that elicit a desired immune response. A vaccine may select, activate or expand memory B and T cells of the immune system to, for example, enable the elimination of infectious agents, such as a SARS virus, or a component thereof. In some embodiments, a vaccine includes a suitable carrier, such as an adjuvant, which is an agent that acts in a non-specific manner to increase the immune response to a specific antigen, or to a group of antigens, enabling the reduction of the quantity of antigen in any given vaccine dose, or the reduction of the frequency of dosage required to generate the desired immune response.

Vaccines according to the invention may include SARS virus polypeptides and nucleic acid molecules described herein, or immunogenic fragments thereof. In some embodiments, a SARS virus Spike polypeptide, Envelope polypeptide, or membrane glycoprotein or fragments thereof may be suitable for vaccine applications. In some

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embodiments, the vaccines may be multivalent and include one or more epitopes from a SARS virus polypeptide or fragment thereof.

In some embodiments of the invention, a vaccine may include a live or killed microorganism e.g., a SARS virus or a component thereof. If a live SARS virus is used, which may be administered in the form of an oral vaccine, is may contain non-revertible genetic alterations (for example, large deletions or insertions in the genomic sequence) that reduce or eliminate the virulence of the virus ("attenuated virus"), but not its induction of an immune response. In some embodiments, a live vaccine may include an attenuated non-SARS microorganism (e.g., bacteria or virus such as vaccinia virus) that is capable of expressing a SARS virus polypeptide or immunogenic fragment thereof as described herein. In some embodiments, a vaccine may include SARS virus polypeptides or nucleic acid molecules having modifications that facilitate ease of administration. For example, an indigestible SARS virus polypeptide or nucleic acid molecule may be used for oral administration, and a modification that is suitable for inhalation may be used for administration to the lung.

A "nucleic acid vaccine" or "DNA vaccine" as used herein, is a nucleic acid construct comprising a polynucleotide encoding a polypeptide antigen, particularly an antigenic amino acid subsequence identified by methods described herein or known in the art. The nucleic acid construct can also include transcriptional promoter elements, enhancer elements, splicing signals, termination and polyadenylation signals, and other nucleic acid sequences. Thus, a nucleic acid vaccine is generally introduced into a subject animal using for example one or more DNA plasmids including one or more antigen-coding sequences (for example, a SARS virus Envelope polypeptide or membrane glycoprotein sequence) that are capable of transfecting cells in vivo and inducing an immune response (see for example Whalen RG et al. DNA-mediated immunization and the energetic immune response to hepatitis B surface antigen. Clin Immunol Immunopathol 1995;75:1-12; Wolff JA et al. Direct gene transfer into mouse muscle in vivo. Science 1990;247:1465-8; Fynan EF et al. DNA vaccines: protective immunizations by parental, mucosal, and genegun inoculations. Proc Natl Acad Sci USA 1993; 90:11478-82). In some embodiments, a library of nucleic acid fragments may be prepared by cloning SARS virus genomic DNA into a plasmid expression vector using known techniques and the library then used as a nucleic acid vaccine (see

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for example Barry MA, et al. Protection against mycoplasma infection using expression-library immunization. Nature 1995;377:632-5).

The subject is administered the nucleic acid vaccine using standard methods. The vertebrate can be administered parenterally, subcutaneously, intravenously, intraperitoneally, intradermally, intramuscularly, topically, orally, rectally, nasally, buccally, vaginally, by inhalation spray, or via an implanted reservoir in dosage formulations containing conventional non-toxic, physiologically acceptable carriers or vehicles. Alternatively, the subject is administered the nucleic acid vaccine through the use of a particle acceleration or bombardment instrument (a "gene gun"). The form in which it is administered (e.g., capsule, tablet, solution, emulsion) will depend in part on the route by which it is administered. For example, for mucosal administration, nose drops, inhalants or suppositories can be used. The nucleic acid vaccine can be administered in conjunction with known adjuvants. The adjuvant is administered in a sufficient amount, which is that amount that is sufficient to generate an enhanced immune response to the nucleic acid vaccine. The adjuvant can be administered prior to (e.g., 1 or more days before) inoculation with the nucleic acid vaccine; concurrently with (e.g., within 24 hours of) inoculation with the nucleic acid vaccine; contemporaneously (simultaneously) with the nucleic acid vaccine (e.g., the adjuvant is mixed with the nucleic acid vaccine, and the mixture is administered to the vertebrate); or after (e.g., 1 or more days after) inoculation with the nucleic acid vaccine. The adjuvant can also be administered at more than one time (e.g., prior to inoculation with the nucleic acid vaccine and also after inoculation with the nucleic acid vaccine). As used herein, the term "in conjunction with" encompasses any time period, including those specifically described herein and combinations of the time periods specifically described herein, during which the adjuvant can be administered so as to generate an enhanced immune response to the nucleic acid vaccine (e.g., an increased antibody titer to the antigen encoded by the nucleic acid vaccine, or an increased antibody titer to the pathogenic agent). The adjuvant and the nucleic acid vaccine can be administered at approximately the same location on the vertebrate; for example, both the adjuvant and the nucleic acid vaccine are administered at a marked site on a limb of the subject.

In some embodiments, expression of a SARS virus gene or coding or noncoding region of interest may be inhibited or prevented using RNA interference (RNAi)

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technology, a type of post-transcriptional gene silencing. RNAi may be used to create a functional "knockout", i.e. a system in which the expression of a gene or coding or non-coding region of interest is reduced, resulting in an overall reduction of the encoded product. As such, RNAi may be performed to target a nucleic acid of interest or fragment or variant thereof, to in turn reduce its expression and the level of activity of the product which it encodes. Such a system may be used for therapy or prophylaxis, as well as for functional studies. RNAi is described in for example published US patent applications 20020173478 (Gewirtz; published November 21, 2002) and 20020132788 (Lewis et al.; published November 7, 2002). Reagents and kits for performing RNAi are available commercially from for example Ambion Inc. (Austin, TX, USA) and New England Biolabs Inc. (Beverly, MA, USA).

The initial agent for RNAi in some systems is thought to be dsRNA molecule corresponding to a target nucleic acid. The dsRNA is then thought to be cleaved into short interfering RNAs (siRNAs) which are 21-23 nucleotides in length (19-21 bp duplexes, each with 2 nucleotide 3' overhangs). The enzyme thought to effect this first cleavage step has been referred to as "Dicer" and is categorized as a member of the Rnase III family of dsRNA-specific ribonucleases. Alternatively, RNAi may be effected via directly introducing into the cell, or generating within the cell by introducing into the cell a suitable precursor (e.g. vector, etc.) of such an siRNA or siRNA-like molecule. An siRNA may then associate with other intracellular components to form an RNA-induced silencing complex (RISC). The RISC thus formed may subsequently target a transcript of interest via base-pairing interactions between its siRNA component and the target transcript by virtue of homology, resulting in the cleavage of the target transcript approximately 12 nucleotides from the 3' end of the siRNA. Thus the target mRNA is cleaved and the level of protein product it encodes is reduced.

RNAi may be effected by the introduction of suitable *in vitro* synthesized siRNA or siRNA-like molecules into cells. RNAi may for example be performed using chemically-synthesized RNA, for which suitable RNA molecules may chemically synthesized using known methods. Alternatively, suitable expression vectors may be used to transcribe such RNA either *in vitro* or *in vivo*. *In vitro* transcription of sense and antisense strands (encoded by sequences present on the same vector or on separate

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vectors) may be effected using for example T7 RNA polymerase, in which case the vector may comprise a suitable coding sequence operably-linked to a T7 promoter. The in vitro-transcribed RNA may in embodiments be processed (e.g. using E. coli RNase III) in vitro to a size conducive to RNAi. The sense and antisense transcripts combined to form an RNA duplex which is introduced into a target cell of interest. Other vectors may be used, which express small hairpin RNAs (shRNAs) which can be processed into siRNA-like molecules. Various vector-based methods are known in the art.

Various methods for introducing such vectors into cells, either in vitro or in vivo (e.g. gene therapy) are known in the art.

Accordingly, in an embodiment, expression of a polypeptide including an amino acid sequence substantially identical to a SARS virus sequence may be inhibited by introducing into or generating within a cell an siRNA or siRNA-like molecule corresponding to a nucleic acid molecule encoding the polypeptide or fragment thereof, or to an nucleic acid homologous thereto. In various embodiments such a method may entail the direct administration of the siRNA or siRNA-like molecule into a cell, or use of the vector-based methods described above. In an embodiment, the siRNA or siRNA-like molecule is less than about 30 nucleotides in length. In a further embodiment, the siRNA or siRNA-like molecules are about 21-23 nucleotides in length. In an embodiment, siRNA or siRNA-like molecules comprise and 19-21 bp duplex portion, each strand having a 2 nucleotide 3' overhang. In embodiments, the siRNA or siRNA-like molecule is substantially identical to a nucleic acid encoding the polypeptide or a fragment or variant (or a fragment of a variant) thereof. Such a variant is capable of encoding a protein having the activity of a SARS virus polypeptide. In embodiments, the sense strand of the siRNA or siRNA-like molecule is substantially identical to a SARS virus nucleic acid molecule or a fragment thereof (RNA having U in place of T residues of the DNA sequence).

#### SARS Virus Protein Expression

In general, SARS virus polypeptides according to the invention, may be produced by transformation of a suitable host cell with all or part of a SARS virus polypeptide-encoding genomic or cDNA molecule or fragment thereof (e.g., the genomic DNA or cDNAs described herein) in a suitable expression vehicle. Those

skilled in the field of molecular biology will understand that any of a wide variety of expression systems may be used to provide the recombinant protein. The precise host cell used is not critical to the invention. The SARS virus polypeptide may be produced in a prokaryotic host (e.g., E. coli or a virus, for example, a coronovirus such as human OC43 or 229E, a bovine coronavirus, or a virus used for gene therapy, such as an adenovirus) or in a eukaryotic host (e.g., Saccharomyces cerevisiae, insect cells, e.g., Sf21cells, or mammalian cells, e.g., COS 1, NIH 3T3, VeroE6, or HeLa cells). Such cells are available from a wide range of sources (e.g., the American Type Culture Collection, Rockland, Md.; also, see, e.g., Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, New York, 1994). The method of transformation or transfection and the choice of expression vehicle will depend on the host system selected. Transformation and transfection methods are described, e.g., in Ausubel et al. (supra); expression vehicles may be chosen from those provided, e.g., in Cloning Vectors: A Laboratory Manual, P. H. Pouwels et al, 1985, Supp. 1987), or from commercially available sources. Suitable animal models, e.g. a ferret animal model, or any other animal model suitable for analysis of SARS virus infection or expression of SARS virus nucleic acid molecules may be used.

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In an alternative embodiment, the baculovirus expression system (using, for example, the vector pBacPAK9) available from Clontech (Pal Alto, Calif.) may be used. If desired, this system may be used in conjunction with other protein expression techniques, for example, the myc tag approach described by Evan et al. (Mol. Cell Biol. 5:3610-3616, 1985). In an alternative embodiment, a SARS virus polypeptide may be produced by a stably-transfected mammalian cell line. A number of vectors suitable for stable transfection of mammalian cells are available to the public, e.g., see Pouwels et al (supra); methods for constructing such cell lines are also publicly available, e.g., in Ausubel et al. (supra). In one example, cDNA encoding the SARS virus polypeptide is cloned into an expression vector which includes the dihydrofolate reductase (DHFR) gene. Integration of the plasmid and, therefore, the SARS virus polypeptide-encoding gene into the host cell chromosome is selected for by inclusion of 0.01-300  $\mu$ M methotrexate in the cell culture medium (as described in Ausubel et al., supra). This dominant selection can be accomplished in most cell types. Recombinant protein expression can be increased by DHFR-mediated amplification of the transfected gene.

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Methods for selecting cell lines bearing gene amplifications are described in Ausubel et al. (supra); such methods generally involve extended culture in medium containing gradually increasing levels of methotrexate. DHFR-containing expression vectors commonly used for this purpose include pCVSEII-DHFR and pAdD26SV(A) (described in Ausubel et al., supra). Any of the host cells described above or, preferably, a DHFR-deficient CHO cell line (e.g., CHO DHFR.sup.- cells, ATCC Accession No. CRL 9096) are among the host cells preferred for DHFR selection of a stably-transfected cell line or DHFR-mediated gene amplification.

Once the recombinant SARS virus polypeptide is expressed, it is isolated, e.g., using affinity chromatography. In one example, an anti-SARS virus polypeptide antibody (e.g., produced as described herein) may be attached to a column and used to isolate the SARS virus polypeptide. Lysis and fractionation of SARS virus polypeptde-harboring cells prior to affinity chromatography may be performed by standard methods (see, e.g., Ausubel et al., supra). In another example, SARS virus polypeptides may be purified or substantially purified from a mixture of compounds such as an extract or supernatant obtained from cells (Ausubel et al., supra). Standard purification techniques can be used to progressively eliminate undesirable compounds from the mixture until a single compound or minimal number of effective compounds has been isolated.

Once isolated, the recombinant protein can, if desired, be further purified, e.g., by high performance liquid chromatography (see, e.g., Fisher, Laboratory Techniques In Biochemistry And Molecular Biology, eds., Work and Burdon, Elsevier, 1980).

Polypeptides of the invention, particularly short SARS virus peptide fragments, can also be produced by chemical synthesis (e.g., by the methods described in Solid Phase Peptide Synthesis, 2nd ed., 1984 The Pierce Chemical Co., Rockford, Ill.).

These general techniques of polypeptide expression and purification can also be used to produce and isolate useful SARSvirus protein fragments or analogs (described herein).

In certain alternative embodiments, the SARS polypeptide might have attached any one of a variety of tags. Tags can be amino acid tags or chemical tags and can be added for the purpose of purification (for example a 6-histidine tag for purification over a nickel column). In other preferred embodiments, various labels can be used as means

for detecting binding of a SARS polypeptide to another polypeptide, for example to a cell surface receptor. Alternatively, SARS DNA or RNA may be labeled for detection, for example in a hybridization assay. SARS virus nucleic acids or proteins, or derivatives thereof, may be directly or indirectly labeled, for example, with a radioscope, a fluorescent compound, a bioluminescent compound, a dhemiluminescent compound, a metal chelator or an enzyme. Those of ordinary skill in the art will know of other suitable labels or will be able to ascertain such, using routine experimentation. In yet another embodiment of the invention, the polypeptides disclosed herein, or derivatives thereof, are linked to toxins.

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### Isolation and Identification of Additional SARS virus molecules

Based on the SARS virus sequences described herein, the isolation and identification of additional SARS virus-related sequences such as SARS virus genes and of additional SARS virus strains or isolates is made possible using standard techniques. In addition, the SARS virus sequences provided herein also provide the basis for identification of homologous sequences from other species and genera from both prokaryotes and eukaryotes such as viruses, bacteria, fungi, parasites, yeast, and/or mammals. In some embodiments, the nucleic acid sequences described herein may be used to design probes or primers, including degenerate oligonucleotide probes or primers, based upon the sequence of either DNA strand. The probes or primers may then be used to screen genomic or cDNA libraries for sequences from for example naturally occurring variants or isolates of SARS viruses, using standard amplification or hybridization techniques.

In some embodiments, binding partners may be identified by tagging the polypeptides of the invention (e.g., those substantially identical to SARS virus polypeptides described herein) with an epitope sequence (e.g., FLAG or 2HA), and delivering it into host cells, either by transfection with a suitable vector containing a nucleic acid sequence encoding a polypeptide of the invention, followed by immunoprecipitation and identification of the binding partner. Cells may be infected with strains expressing the FLAG or 2HA fusions, followed by lysis and immunoprecipitation with anti-FLAG or anti-2HA antibodies. Binding partners may be identified by mass spectroscopy. If the polypeptide of the invention is not produced in

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sufficient quantities, such a method may not deliver enough tagged protein to identify its partner. As part of a complementary approach, each polypeptide of the invention may be cloned into a mammalian transfection vector fused to, for example, 2HA, GFP and/or FLAG. Following transfection, HeLa cells may be lysed and the tagged polypeptide immunoprecipitated. The binding partner may be identified by SDS PAGE followed by mass spectroscopy.

In some embodiments, polypeptides or antibodies of the invention may be tagged, produced, and used for example on affinity columns and/orin immunological assays to identify and/or confirm identified target compounds. FLAG, HA, and/or His tagged proteins can be used for such affinity columns to pull out host cell factors from cell extracts, and any hits may be validated by standard binding assays, saturation curves, and other methods as described herein or known to those of skill in the art.

In some embodiments, a two hybrid system may be used to study protein-protein interactions. The nucleic acid sequences described herein, or sequences substantially identical thereto, can be cloned into the pBT bait plasmid of the two hybrid system, and a commercially available murine spleen library of 5 x 10<sup>6</sup> independent clones, may be used as the target library for the baits. Potential hits may be further characterized by recovering the plasmids and retransforming to reduce false positives resulting from clonal bait variants and library target clones which activate the reporter genes independent of the cloned bait. Reproducible hits may be studied further as described herein.

Virulence may be assayed as described herein or as known to those of skill in the art. Once coding sequences have been identified, they may be isolated using standard cloning techniques, and inserted into any suitable vector or replicon for, for example, production of polypeptides. Such vectors and replicons include, without limitation, bacteriophage X (E. coli), pBR322 (E. coli), pACYC177 (E. coli), pKT230 (gramnegative bacteria), pGV1 106 (gramnegative bacteria), pLAFRI (gramnegative bacteria), pME290 (non-E. coli gramnegative bacteria), pHV14 (E. coli and Bacillus subtilis), pBD9 (Bacillus), pIJ61 (Streptomyces), pUC6 (Streptomyces), YIp5 (Saccharomyces), YCpl9 (Saccharomyces) or bovine papilloma virus (mammalian cells). In general, the polypeptides of the invention may be produced in any suitable host cell transformed or transfected with a suitable vector. The method of

transformation or transfection and the choice of expression vehicle will depend on the host system selected. A wide variety of expression systems may be used, and the precise host cell used is not critical to the invention. For example, a polypeptide according to the invention may be produced in a prokaryotic host (e.g., *E. coli*) or in a eukaryotic host (e.g., *Saccharomyces cerevisiae*, insect cells, e.g., Sf21 cells, or mammalian cells, e.g., NIH 3T3, HeLa, or COS cells). Such cells are available from a wide range of sources (e.g., the American Type Culture Collection, Manassus, VA.). Bacterial expression systems for polypeptide production include the E. coli pET expression system (Novagen, Inc., Madison, Wis.), and the pGEX expression system(Pharmacia).

## Compounds

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In one aspect, compounds according to the invention include SARS virus nucleic acid molecules and polypeptides, such as the sequences disclosed in the Figures and Tables herein, and throughout the specification, and fragments thereof. In alternative embodiments, compounds according to the invention may be nucleic acid molecules that are at least 10 nucleotides in length, and that are derived from the sequences described herein. In alternative embodiments, compounds according to the invention may be peptides that are at least 5 amino acids in length, and that are derived from the sequences described herein.

In alternative embodiments, a compound according to the invention can be a non-peptide molecule as well as a peptide or peptide analogue. A peptide or peptide analogue will generally be as small as feasible while retaining full biological activity. A non-peptide molecule can be any molecule that exhibits biological activity as described herein or known in the art. Biological activity can, for example, be measured in terms of ability to elicit a cytotoxic response, to mediate DNA replication, or any other function of a SARS virus molecule.

Compounds can be prepared by, for example, replacing, deleting, or inserting an amino acid residue of SARS peptide or peptide analogue, as described herein, with other conservative amino acid residues, i.e., residues having similar physical, biological, or chemical properties, and screening for biological function.

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It is well known in the art that some modifications and changes can be made in the structure of a polypeptide without substantially altering the biological function of that peptide, to obtain a biologically equivalent polypeptide. Such modifications may be made for the purpose of modifying function, or for facilitating administration or enhancing stability or inhibiting breakdown for, for example, therapeutic uses. For example, an indigestible SARS virus compound according to the invention may be used for oral administration; a modification that is suitable for inhalation may be used for administration to the lung; or addition of a leader sequence may increase protein expression levels.

In one aspect of the invention, SARS virus-derived peptides or epitopes may include peptides that differ from a portion of a native leader, protein or SARS virus sequence by conservative amino acid substitutions. The peptides and epitopes of the present invention also extend to biologically equivalent peptides that differ from a portion of the sequence of novel peptides of the present invention by conservative amino acid substitutions. As used herein, the term "conserved amino acid substitutions" refers to the substitution of one amino acid for another at a given location in the peptide, where the substitution can be made without substantial loss of the relevant function. In making such changes, substitutions of like amino acid residues can be made on the basis of relative similarity of side-chain substituents, for example, their size, charge, hydrophobicity, hydrophilicity, and the like, and such substitutions may be assayed for their effect on the function of the peptide by routine testing.

In some embodiments, conserved amino acid substitutions may be made where an amino acid residue is substituted for another having a similar hydrophilicity value (e.g., within a value of plus or minus 2.0), where the following may be an amino acid having a hydropathic index of about -1.6 such as Tyr (-1.3) or Pro (-1.6)s are assigned to amino acid residues (as detailed in United States Patent No. 4,554,101, incorporated herein by reference): Arg (+3.0); Lys (+3.0); Asp (+3.0); Glu (+3.0); Ser (+0.3); Asn (+0.2); Gln (+0.2); Gly (0); Pro (-0.5); Thr (-0.4); Ala (-0.5); His (-0.5); Cys (-1.0); Met (-1.3); Val (-1.5); Leu (-1.8); Ile (-1.8); Tyr (-2.3); Phe (-2.5); and Trp (-3.4).

In alternative embodiments, conserved amino acid substitutions may be made where an amino acid residue is substituted for another having a similar hydropathic index (e.g., within a value of plus or minus 2.0). In such embodiments, each amino acid

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residue may be assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics, as follows: Ile (+4.5); Val (+4.2); Leu (+3.8); Phe (+2.8); Cys (+2.5); Met (+1.9); Ala (+1.8); Gly (-0.4); Thr (-0.7); Ser (-0.8); Trp (-0.9); Tyr (-1.3); Pro (-1.6); His (-3.2); Glu (-3.5); Gln (-3.5); Asp (-3.5); Asn (-3.5); Lys (-3.9); and Arg (-4.5).

In alternative embodiments, conserved amino acid substitutions may be made where an amino acid residue is substituted for another in the same class, where the amino acids are divided into non-polar, acidic, basic and neutral classes, as follows: non-polar: Ala, Val, Leu, Ile, Phe, Trp, Pro, Met; acidic: Asp, Glu; basic: Lys, Arg, His; neutral: Gly, Ser, Thr, Cys, Asn, Gln, Tyr.

Conservative amino acid changes can include the substitution of an L-amino acid by the corresponding D-amino acid, by a conservative D-amino acid, or by a naturally-occurring, non-genetically encoded form of amino acid, as well as a conservative substitution of an L-amino acid. Naturally-occurring non-genetically encoded amino acids include beta-alanine, 3-amino-propionic acid, 2,3-diamino propionic acid, alpha-aminoisobutyric acid, 4-amino-butyric acid, N-methylglycine (sarcosine), hydroxyproline, ornithine, citrulline, t-butylalanine, t-butylglycine, N-methylisoleucine, phenylglycine, cyclohexylalanine, norleucine, norvaline, 2-napthylalanine, pyridylalanine, 3-benzothienyl alanine, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, penicillamine, 1,2,3,4-tetrahydro-isoquinoline-3-carboxylix acid, beta-2-thienylalanine, methionine sulfoxide, homoarginine, N-acetyl lysine, 2-amino butyric acid, 2-amino butyric acid, 2,4,-diamino butyric acid, p-aminophenylalanine, N-methylvaline, homocysteine, homoserine, cysteic acid, epsilon-amino hexanoic acid, delta-amino valeric acid, or 2,3-diaminobutyric acid.

In alternative embodiments, conservative amino acid changes include changes based on considerations of hydrophilicity or hydrophobicity, size or volume, or charge. Amino acids can be generally characterized as hydrophobic or hydrophilic, depending primarily on the properties of the amino acid side chain. A hydrophobic amino acid exhibits a hydrophobicity of greater than zero, and a hydrophilic amino acid exhibits a hydrophilicity of less than zero, based on the normalized consensus hydrophobicity scale of Eisenberg *et al.* (*J. Mol. Bio.* 179:125-142, 184). Genetically encoded

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hydrophobic amino acids include Gly, Ala, Phe, Val, Leu, Ile, Pro, Met and Trp, and genetically encoded hydrophilic amino acids include Thr, His, Glu, Gln, Asp, Arg, Ser, and Lys. Non-genetically encoded hydrophobic amino acids include t-butylalanine, while non-genetically encoded hydrophilic amino acids include citrulline and homocysteine.

Hydrophobic or hydrophilic amino acids can be further subdivided based on the characteristics of their side chains. For example, an aromatic amino acid is a hydrophobic amino acid with a side chain containing at least one aromatic or heteroaromatic ring, which may contain one or more substituents such as –OH, -SH, -CN, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -NO, -NH<sub>2</sub>, -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, -C(O)NH<sub>2</sub>, -C(O)NHR, -C(O)NRR, etc., where R is independently (C<sub>1</sub>-C<sub>6</sub>) alkyl, substituted (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>1</sub>-C<sub>6</sub>) alkenyl, substituted (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>1</sub>-C<sub>6</sub>) alkynyl, substituted (C<sub>5</sub>-C<sub>20</sub>) aryl, substituted (C<sub>5</sub>-C<sub>20</sub>) aryl, (C<sub>6</sub>-C<sub>26</sub>) alkaryl, substituted (C<sub>6</sub>-C<sub>26</sub>) alkaryl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl. Genetically encoded aromatic amino acids include Phe, Tyr, and Tryp, while non-genetically encoded aromatic amino acids include Phenylglycine, 2-napthylalanine, beta-2-thienylalanine, 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, 4-chlorophenylalanine, 2-fluorophenylalanine3-fluorophenylalanine, and 4-fluorophenylalanine.

An apolar amino acid is a hydrophobic amino acid with a side chain that is uncharged at physiological pH and which has bonds in which a pair of electrons shared in common by two atoms is generally held equally by each of the two atoms (i.e., the side chain is not polar). Genetically encoded apolar amino acids include Gly, Leu, Val, Ile, Ala, and Met, while non-genetically encoded apolar amino acids include cyclohexylalanine. Apolar amino acids can be further subdivided to include aliphatic amino acids, which is a hydrophobic amino acid having an aliphatic hydrocarbon side chain. Genetically encoded aliphatic amino acids include Ala, Leu, Val, and Ile, while non-genetically encoded aliphatic amino acids include norleucine.

A polar amino acid is a hydrophilic amino acid with a side chain that is uncharged at physiological pH, but which has one bond in which the pair of electrons shared in common by two atoms is held more closely by one of the atoms. Genetically

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encoded polar amino acids include Ser, Thr, Asn, and Gln, while non-genetically encoded polar amino acids include citrulline, N-acetyl lysine, and methionine sulfoxide.

An acidic amino acid is a hydrophilic amino acid with a side chain pKa value of less than 7. Acidic amino acids typically have negatively charged side chains at physiological pH due to loss of a hydrogen ion. Genetically encoded acidic amino acids include Asp and Glu. A basic amino acid is a hydrophilic amino acid with a side chain pKa value of greater than 7. Basic amino acids typically have positively charged side chains at physiological pH due to association with hydronium ion. Genetically encoded basic amino acids include Arg, Lys, and His, while non-genetically encoded basic amino acids include the non-cyclic amino acids ornithine, 2,3,-diaminopropionic acid, 2,4-diaminobutyric acid, and homoarginine.

It will be appreciated by one skilled in the art that the above classifications are not absolute and that an amino acid may be classified in more than one category. In addition, amino acids can be classified based on known behaviour and or characteristic chemical, physical, or biological properties based on specified assays or as compared with previously identified amino acids. Amino acids can also include bifunctional moieties having amino acid-like side chains.

Conservative changes can also include the substitution of a chemically derivatised moiety for a non-derivatised residue, by for example, reaction of a functional side group of an amino acid. Thus, these substitutions can include compounds whose free amino groups have been derivatised to amine hydrochlorides, ptoluene sulfonyl groups, carbobenzoxy groups, t-butyloxycarbonyl groups, chloroacetyl groups or formyl groups. Similarly, free carboxyl groups can be derivatized to form salts, methyl and ethyl esters or other types of esters or hydrazides, and side chains can be derivatized to form O-acyl or O-alkyl derivatives for free hydroxyl groups or N-imbenzylhistidine for the imidazole nitrogen of histidine. Peptide analogues also include amino acids that have been chemically altered, for example, by methylation, by amidation of the C-terminal amino acid by an alkylamine such as ethylamine, ethanolamine, or ethylene diamine, or acylation or methylation of an amino acid side chain (such as acylation of the epsilon amino group of lysine). Peptide analogues can also include replacement of the amide linkage in the peptide with a substituted amide

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The compound can be covalently linked, for example, by polymerisation or conjugation, to form homopolymers or heteropolymers. Spacers and linkers, typically composed of small neutral molecules, such as amino acids that are uncharged under physiological conditions, can be used. Linkages can be achieved in a number of ways. For example, cysteine residues can be added at the peptide termini, and multiple peptides can be covalently bonded by controlled oxidation. Alternatively, heterobifunctional agents, such as disulfide/amide forming agents or thioether/amide forming agents can be used. The compound can also be constrained, for example, by having cyclic portions.

In some embodiments, three dimensional molecular modeling techniques may be used to identify or generate compounds that may be useful as therapeutics or diagnostics. Standard molecular modeling tools may be used, for example, those described in L-H Hung and R. Samudrala, PROTINFO: secondary and tertiary protein structure prediction, Nucleic Acids Research, 2003, Vol. 31, No. 13 3296-3299; A. Yamaguchi, et al., Enlarged FAMSBASE: protein 3D structure models of genome sequences for 41 species, Nucleic Acids Research, 2003, Vol. 31, No. 1 463-468; J. Chen, et al., MMDB: Entrez's 3D-structure database, Nucleic Acids Research, 2003, Vol. 31, No. 1 474-477; R. A. Chiang, et al., The Structure Superposition Database, Nucleic Acids Research, 2003, Vol. 31, No. 1 505-510.

Peptides or peptide analogues can be synthesized by standard chemical

techniques, for example, by automated synthesis using solution or solid phase synthesis
methodology. Automated peptide synthesizers are commercially available and use
techniques well known in the art. Peptides and peptide analogues can also be prepared
using recombinant DNA technology using standard methods such as those described in,
for example, Sambrook, et al. (Molecular Cloning: A Laboratory Manual. 2.sup.nd, ed.,
Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring
Harbor, N.Y., 1989) or Ausubel et al. (Current Protocols in Molecular Biology, John
Wiley & Sons, 1994).

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Compounds, such as peptides (or analogues thereof) can be identified by routine experimentation by, for example, modifying residues within SARS peptides; introducing single or multiple amino acid substitutions, deletions, or insertions, and identifying those compounds that retain biological activity, e.g., those compounds that have cytotoxic ability.

In general, candidate compounds for prevention or treatment of SARS virusmediated disorders are identified from large libraries of both natural product or
synthetic (or semi-synthetic) extracts or chemical libraries according to methods known
in the art. Candidate or test compounds may include, without limitation, peptides,
polypeptides, synthesised organic molecules, naturally occurring organic molecules,
and nucleic acid molecules. In some embodiments, such compounds screen for the
ability to inhibit SARS virus replication or pathogenicity, while maintaining the
infected cell's ability to grow or survive.

Those skilled in the field of drug discovery and development will understand that the precise source of test extracts or compounds is not critical to the method(s) of the invention. Accordingly, virtually any number of chemical extracts or compounds can be screened using the exemplary methods described herein or using standard methods. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic- or animal-based extracts, fermentation broths, and synthetic compounds, as well as modification of existing compounds. Numerous methods are also available for generating random or directed synthesis (e.g., semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid-based compounds. Synthetic compound libraries are commercially available. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova (Slough, UK), Harbor Branch Oceanographic Institute (Ft. Pierce, Fla.), and PharmaMar, U.S.A. (Cambridge, Mass.). In addition, natural and synthetically produced libraries of, for example, SARS virus polypeptides containing leader sequences, are produced, if desired, according to methods known in the art, e.g., by standard extraction and fractionation methods. Furthermore, if desired, any library or compound is readily modified using standard chemical, physical, or biochemical methods.

When a crude extract is found to modulate cytotoxicity or viral infection, further fractionation of the positive lead extract is necessary to isolate chemical constituents responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and identification of a chemical entity within the crude extract having, for example, anti-cytotoxicity or anti-viral properties. The same assays described herein for the detection of activities in mixtures of compounds can be used to purify the active component and to test derivatives thereof. Methods of fractionation and purification of such heterogenous extracts are known in the art. If desired, compounds shown to be useful agents for treatment are chemically modified according to methods known in the art. Compounds identified as being of therapeutic, prophylactic, diagnostic, or other value in for example cell culture systems, such as a Vero E6 culture system, may be subsequently analyzed using a ferret animal model, or any other animal model suitable for analysis of SARS.

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#### **Antibodies**

The compounds of the invention can be used to prepare antibodies to SARS virus peptides, protein, polyproteins, or analogs thereof, or to SARS virus nucleic acid molecules or analogs thereof using standard techniques of preparation as, for example, described in Harlow and Lane (Antibodies; A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1988), or known to those skilled in the art. Antibodies may include polyclonal antibodies, monoclonal antibodies, hybrid antibodies (e.g., divalent antibodies having different pairs of heavy and light chains), chimeric antibodies (e.g., antibodies having constant and variable domains from different species and/or class), modified antibodies (e.g., antibodies in which the naturally occurring sequence has been altered by for example recombinant techniques), Fab antibodies, anti-idiotype antibodies, etc. Antibodies can be tailored to minimise adverse host immune response by, for example, using chimeric antibodies containing an antigen binding domain from one species and the Fc portion from another species, or by using antibodies made from hybridomas of the appropriate species. For example, "humanized" antibodies may be used for administration to humans.

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To generate SARS virus polypeptide-specific antibodies, a SARS virus polypeptide coding sequence may be expressed, for example, as a C-terminal fusion with glutathione S-transferase (GST) (Smith et al., Gene 67:31-40, 1988). The fusion polypeptide may then be purified on glutathione-Sepharose beads, eluted with glutathione cleaved with thrombin (at the engineered cleavage site), and purified to the degree necessary for immunization of rabbits. Primary immunizations are carried out with Freud's complete adjuvant and subsequent immunizations with Freud's incomplete adjuvant. Antibody titres are monitored by Western blot and immunoprecipitation analyzes using the thrombin-cleaved SARS virus polypeptide fragment of the GST-SARS virus fusion polypeptide. Immune sera are affinity purified using CNBr-Sepharose-coupled SARS virus polypeptide. Antiserum specificity is determined using a panel of unrelated GST polypeptides.

As an alternate or adjunct immunogen to GST fusion polypeptides, peptides corresponding to relatively unique hydrophilic SARS virus polypeptides may be generated and coupled to keyhole limpet hemocyanin (KLH) through an introduced C-terminal lysine. Antiserum to each of these peptides is similarly affinity purified on peptides conjugated to BSA, and specificity tested in ELISA and Western blots using peptide conjugates, and by Western blot and immunoprecipitation using SARS virus polypeptide expressed as a GST fusion polypeptide.

Alternatively, monoclonal antibodies may be prepared using the SARS virus polypeptides described above and standard hybridoma technology (see, e.g., Kohler et al., Nature, 256:495, 1975; Kohler et al., Eur. J Immunol. 6:511, 1976; Kohler et al., Eur. J. Immunol. 6:292, 1976; Hammerling et al., In Monoclonal Antibodies and T Cell Hybridomas, Elsevier, NY, 1981; Ausubel et al., supra). Once produced, monoclonal antibodies are also tested for specific SARS virus polypeptide recognition by Western blot or immunoprecipitation analysis (by the methods described in Ausubel et al., supra). Antibodies which specifically recognize SARS virus polypeptides are considered to be useful in the invention; such antibodies may be used, e.g., in an immunoassay to monitor the level of SARS virus polypeptides produced by a mammal (for example, to determine the amount or location of a SARS virus polypeptide).

In an alternative embodiment, antibodies of the invention are not only produced using the whole SARS virus polypeptide, but using fragments of the SARS virus

polypeptide which are unique or which lie outside highly conserved regions and appear likely to be antigenic, by criteria such as high frequency of charged residues may also be used. In one specific example, such fragments are generated by standard techniques of PCR and cloned into the pGEX expression vector (Ausubel et al., supra). Fusion polypeptides are expressed in E. coli and purified using a glutathione agarose affinity matrix as described in Ausubel et al. (supra). To attempt to minimize the potential problems of low affinity or specificity of antisera, two or three such fusions are generated for each polypeptide, and each fusion is injected into at least two rabbits. Antisera are raised by injections in a series, preferably including at least three booster injections. SARS virus antibodies may also be prepared against SARS virus nucleic acid molecules.

Antibodies may be used as diagnostics, therapeutics, or prophylactics for SARS virus-related disorders. Antibodies may also be used to isolate SARS virus and compounds by for example affinity chromatography, or to identify SARS virus compounds isolated or generated by other techniques.

#### Arrays and Libraries

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In some aspects, biological assays, such as diagnostic or other assays, using high density nucleic acid, polypeptide, or antibody arrays, for example high density miniaturized arrays or "microarrays," of SARS virus nucleic acid molecules or polypeptides, or antibodies capable of specifically binding such nucleic acid molecules or polypeptides, may be performed. Macroarrays, performed for example by manual spotting techniques, may also be used. Arrays generally require a solid support (for example, nylon, glass, ceramic, plastic, silicon, nitrocellulose or PVDF membranes, microwells, microbeads, e.g., magnetic microbeads, etc.) to which the nucleic acid molecules or polypeptides or antibodies are attached in a specified two-dimensional arrangement, such that the pattern of hybridization is easily determinable. Suspension arrays (particles in suspension) that are coded to facilitate identification may also be used. SARS virus nucleic acid molecules or polypeptide probes or targets may be compounds as described herein.

In some embodiments, high density nucleic acid arrays may for example be used to monitor the presence or level of expression of a large number of SARS virus

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nucleic acid molecules or genes or for detecting or identifying SARS virus nucleic acid sequence variations, mutations or polymorphisms. For the purpose of such arrays, "nucleic acids" may include any polymer or oligomer of nucleosides or nucleotides (polynucleotides or oligonucleotides), which include pyrimidine and purine bases, preferably cytosine, thymine, and uracil, and adenine and guanine, respectively, or may include peptide nucleic acids (PNA). In an alternative aspect, the invention provides nucleic acid microarrays including a number of distinct nucleic acid sequence arrays of the invention, thus providing specific "sets" of sequences. The number of distinct sequences may for example be any integer between 2 and 1 x 10<sup>5</sup>, such as at least 10<sup>2</sup>, 10<sup>3</sup>, 10<sup>4</sup>, or 10<sup>5</sup>.

The invention also provides gene knockout and expression libraries. Thus, nucleic acid molecules encoding SARS virus polypeptides or proteins (e.g., PCR products of ORF's or total mRNA) may for example be attached to a solid support, hybridized with single stranded detectably-labeled cDNAs (corresponding to an "antisense" orientation), and quantified using an appropriate method such that a signal is detected at each location at which hybridization has taken place. The intensity of the signal would then reflect the level of gene expression. Comparison of results from viruses, for example, of different strains or from different samples or subjects, would elucidate differing levels of expression of specified genes. Using similar techniques, homologous nucleic acids may be identified from different viruses if SARS virus nucleic acids are used in the microarray, and probed with nucleic acid molecules from different viruses or subjects. In some embodiments, this approach may involve constructing his-tagged ORF expression libraries of viral genomes in a bacterial host, similar to an expression library in yeast (Martzen M. R. et al., 1999. Science, 286:1153). ORF-encoded protein activities may for example be detected in purified histagged protein pools in cases where activities cannot be detected in extracts or cells. In one aspect of the invention, arrayed libraries may be constructed of viral strains each of which bears a plasmid expressing a different SARS virus ORF under control of an inducible promoter. ORFs are amplified using PCR and cloned into a vector that enables their expression as N-terminal his-tagged polypeptides. These amplicons are also used to construct hybridization microarrays and enable targeted gene disruption, reducing expenses. A suitable expression host is selected, and genes encoding

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particular biochemical activities are identified by screening arrayed pools of his-tagged proteins as described previously (Martzen M. R., McCraith S. M., Spinelli S.L., Torres F. M., Fields S., Grayhack E.J., and Phizicky E. M., 1999. Science, 286:1153).

In some embodiments, protein arrays (including antibody or antigen arrays) may be used for the analysis and identification of SARS virus polypeptides or host responses to such polypeptides. Thus, protein arrays may be used to detect SARS virus polypeptides in a patient; distinguish a SARS virus polypeptide from a host polypeptide; detect interactions between SARS virus polypeptides and for example host proteins; determine the efficacy of potential therapeutics, such as small molecules or ligands that may bind SARS virus polypeptides; determine protein-antibody interactions; and/or detect the interaction of enzyme-substrate interactions. Protein arrays may also be used to detect SARS virus antigens and antibodies in samples; to profile expression of SARS virus polypeptides; to identify suitable antibodies or map epitopes; or for a variety of protein function analyses.

15 A variety of methods are known for making and using microarrays, as for example disclosed in Cheung V. G., et al., 1999. Nature Genetics Supplement, 21:15-19; Lipshutz R. J., et al., 1999. Nature Genetics Supplement, 21:20-24; Bowtell D. D. L., 1999. Nature Genetics Supplement, 21:25-32; Singh-Gasson S., et al., 1999. Nature Biotechnol., 17:974-978; and Schweitzer B., et al., 2002. Nature Biotechnol., 20:359-365. Thus, for example, microarrays may be designed by synthesizing 20 oligonucleotides with sequence variations based on a reference sequences, such as any SARS virus sequences described herein. Methods for storing, querying and analyzing microarray data have for example been disclosed in, for example, United States Patent No. 6,484,183; United States Patent No. 6,188,783; and Holloway A. J., et al., 2002. Nature Genetics Supplement, 32:481-489. Protein arrays may be constructed, detected, 25 and analysed using methods known in the art for example mass spectrometric techniques, immunoassays such as ELISA and western (dot) blotting combined with for example fluorescence detection techniques, and adapted for high throughput analysis, as described in for example MacBeath, G. and Schreiber, S.L. Science 2000, 289, 1760-1763; Levit-Binnun N, et al. (2003) Quantitative detection of protein arrays. Anal 30 Chem 75:1436-41; Kukar T, et al. (2002) Protein microarrays to detect protein-protein interactions using red and green fluorescent proteins. Anal Biochem 306:50-4;

Borrebaeck CA, et al. (2001) Protein chips based on -recombinant antibody fragments: a highly sensitive approach as detected by mass spectrometry. Biotechniques 30:1126-1132; Huang RP (2001) Detection of multiple proteins in an antibody-based protein microarray system. J Immunol Methods 255:1-13; Emili AQ and Cagney G (2000) Large-scale functional analysis using peptide or protein arrays. Nature Biotechnol 18:393-397; Zhu H, et al. (2000) Analysis of yeast protein kinases using protein chips. Nature Genet 26:283-9; Lucking A, et al. (1999) Protein Microarrays for Gene Expression and Antibody Screening. Anal. Biochem. 270:103-111; or Templin MF, et al. (2002) Protein microarray technology. Drug Discov Today 7:815-822. Tools for 10 microarray techniques are available commercially from for example Affymetrix, Santa Clara, CA; Nanogen, San Diego, CA; or Sequenom, San Diego, CA.

## Computer Readable Records

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Nucleic acid and polypeptide sequences, as described herein, or a fragment thereof, may be provided in a variety of media to facilitate access to these sequences and enable the use thereof. According, SARS virus nucleic acid and polypeptide sequences of the invention may be recorded or stored on computer readable media, using any technique and format that is appropriate for the particular medium.

In alternative embodiments, the invention provides computer readable media encoded with a number of distinct nucleic acid or amino acid data sequences of the invention. The number of distinct sequences may for example be any integer between 2 and 1 x 10<sup>5</sup>, such as at least 10<sup>2</sup>, 10<sup>3</sup>, 10<sup>4</sup>, or 10<sup>5</sup>. In one embodiment, the invention features a computer medium having a plurality of digitally encoded data records. Each data record may include a value representing a nucleic acid or amino acid sequence of the invention. In some embodiments, the data record may further include values representing the level of expression, level or activity of a nucleic acid or amino acid sequence of the invention. The data record can be structured as a table, for example, a table that is part of a database such as a relational database (for example, a SQL database of the Oracle or Sybase database environments). The invention also includes a method of communicating information about a sample, for example by transmitting information, for example transmitting a computer readable record as described herein, for example over a computer network. The polypeptide and nucleic acid sequences of

the invention, and sequence information pertaining thereto, may be routinely accessed by one of ordinary skill in the art for a variety of purposes, including for the purposes of comparing substantially identical sequences, etc. Such access may be facilitated using publicly available software as described herein. By "computer readable media" is meant any medium that can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media.

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## Pharmaceutical and Veterinary Compositions, Dosages, And Administration

Compounds of the invention can be provided alone or in combination with other compounds (for example, small molecules, peptides, or peptide analogues), in the presence of a liposome, an adjuvant, or any pharmaceutically acceptable carrier, in a form suitable for administration to humans or to animals.

Conventional pharmaceutical practice may be employed to provide suitable formulations or compositions to administer the compounds to patients suffering from or presymptomatic for SARS. Any appropriate route of administration may be employed, for example, parenteral, intravenous, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, or oral administration. In some embodiments, compounds are delivered directly to the lung, by for example, formulations suitable for inhalation. In some embodiments, gene therapy techniques may be used for administration of SARS virus nucleic acid molecules, for example, as DNA vaccines. Formulations may be in the form of liquid solutions or suspensions; for oral administration, formulations may be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

Methods well known in the art for making formulations are found in, for example, "Remington's Pharmaceutical Sciences" (18<sup>th</sup> edition), ed. A. Gennaro, 1990, Mack Publishing Company, Easton, Pa. Formulations for parenteral administration may, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated napthalenes.

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Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems for modulatory compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

If desired, treatment with a compound according to the invention may be combined with more traditional therapies for the disease.

For therapeutic or prophylactic compositions, the compounds are administered to an individual in an amount sufficient to stop or slow the replication of the SARS virus, or to confer protective immunity against future SARS virus infection. Amounts considered sufficient will vary according to the specific compound used, the mode of administration, the stage and severity of the disease, the age, sex, and health of the individual being treated, and concurrent treatments. As a general rule, however, dosages can range from about  $1\mu g$  to about 100 mg per kg body weight of a patient for an initial dosage, with subsequent adjustments depending on the patient's response, which can be measured, for example by determining the presence of SARS nucleic acid molecules, polypeptides, or virions in the patient's peripheral blood.

In the case of vaccine formulations, an immunogenically effective amount of a compound of the invention can be provided, alone or in combination with other compounds, with an adjuvant, for example, Freund's incomplete adjuvant or aluminum hydroxide. The compound may also be linked with a carrier molecule, such as bovine serum albumin or keyhole limpet hemocyanin to enhance immunogenicity. In general, compounds of the invention should be used without causing substantial toxicity. Toxicity of the compounds of the invention can be determined using standard techniques, for example, by testing in cell cultures or experimental animals and determining the therapeutic index, i.e., the ratio between the LD50 (the dose lethal to 50% of the population) and the LD100 (the dose lethal to 100% of the population). In some circumstances however, such as in severe disease conditions, it may be necessary to administer substantial excesses of the compositions.

#### Virus Isolation

Virus isolation was performed on a bronchoaveolar lavage specimen of a fatal SARS case belonging to the original case cluster from Toronto, Canada. All work with the infectious agent was performed in a biosafety level 3 (BSL3) laboratory using a 5 N100 mask for personal protection. Samples were removed from BSL3 after addition of the RNA extraction buffer. The virus isolate, named the "Tor2 isolate" was grown in African Green Monkey Kidney (Vero E6) cells, the viral particles were purified, and the genetic material (RNA) was extracted from the Tor2 isolate (Poutanen, S. M. et al., N Engl J Med, Apr 10, 2003). More specifically, one hundred microlitre specimens 10 were used to inoculate Vero E6 cells (ATCC CRL 1586) on Dulbecco's Modified Eagle Medium supplemented with penicillin/ streptomycin, glutamine and 2% fetal calf serum. The culture was incubated at 37°C. Cytopathogenic effect was observed 5 days post inoculation. The virus was passaged into newly seeded Vero E6 cells which showed a cytopathogenic effect as early as 2 days post infection (multiplicity of 15 infection 10<sup>-2</sup>). A virus stock was prepared from passage 2 of these cells and preserved in liquid nitrogen. The titer of the virus stock was determined to be 1x10<sup>7</sup> plaque forming units (p.f.u.) by plaque assay and 5 x 10<sup>6</sup> by tissue culture infectious dose (TCID) 50.

For virus propagation,  $10 \times T-162$  flasks of Vero E6 cells were infected with a multiplicity of infection of  $10^{-2}$ . When infected cells showed a cytopathognic effect of '4+' (48 hours post infection), the cultures were then frozen and thawed to lyse the cells, and the supernatants were clarified from cell debris by centrifugation at 10,000 rpm in a Beckman high-speed centrifuge. The supernatants were treated with DNAse and RNAse for 3 hours at 37°C to remove any cellular genomic nucleic acids and subsequently extracted with an equal volume of 1,1,2-trichloro-trifluoroethane. The top fraction was ultra-centrifuged through a 5% / 40% glycerol step gradient at 151,000 x g for 1 hour at 4°C. The virus pellet was resuspended in PBS. RNA was isolated using a commercial kit from QIAGEN and stored at -80°C for further use.

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Size-selected cDNA products were cloned and single sequence reads were generated from each end of the insert from randomly picked clones. A list of the SARS virus clones is provided in the accompanying sequence listing, which is incorporated by reference herein (SEQ ID NOs: 92-159, 208 and 209).

More specifically, size-selected cDNAs were ligated into the pCR4-TOPO TA cloning vector (Invitrogen, CA), or after digestion with the restriction nuclease Not I into the pBR194c vector (The Institute for Genomic Research, Rockville, MD, USA). Ligated clones were then transformed by electroporation into DH10B T1 cells (Invitrogen), plated on 22 cm agar plates with the appropriate antibiotic and grown for 16 hours at 37°C. Colonies were picked into 384-well Axygen culture blocks containing 2 X YT media and grown in a shaking incubator for 18 hours at 37°C. Cells were lysed and DNA purified using standard laboratory procedures. Sequencing primers for the 194c clones were 5'-GGCCTCTTCGCTATTACGC-3' (forward primer) and 5' TGCAGGTCGACTCTAGAGGAT-3' (reverse primer).

# DNA Sequencing And Assembly Of Reads

Sequences were assembled and the assembly edited to produce the genomic sequence of the SARS virus. More specifically, DNA sequencing of both ends of the plasmid templates was achieved using Applied Biosystems BigDye terminator reagent

(version 3), with electrophores and data collection on AB 3700 and 3730 XL instruments DNA sequence reads were screened for non-viral contaminating sequences, trimmed for quality using PHRED (Ewing, B, and P. Green, *Genome Res* 8, 186-94, Mar, 1998) and assembled using PHRAP (Gordon, D. et al. *Genome Res* 8, 195-202, Mar, 1998). Simultaneously, sequences were used in BLAST searches of viral nucleotide and non-redundant protein datasets (NCBI, National Library of Medicine) to search for similarities. Sequence assemblies were visualized using CONSED (Gordon, D. et al. *Genome Res* 8, 195-202, Mar, 1998). Sequence misassemblies and contig joins were identified using Miropeats (Parsons, J. D., *Comput Appl Biosci* 11, 615-9 (Dec, 1995). As sequence data accrued, the additional sequences were assembled until it became apparent that the additional depth of sampling was increasing depth of coverage but not extending the length of the contig. At this point, 3,080 sequencing reads were generated, 2,634 of which were assembled into a single large contig.

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The sequence information was imported into an ACEDB database (Durbin, J. Thierry-Mieg. 1991-. A C. elegans Database. Documentation, code and data available from anonymous FTP servers at lirmm.lirmm.fr, cele.mrc-lmb.cam.ac.uk and ncbi.nlm.nih.gov) and subjected to biological analysis including the identification of open reading frames, detection of similar sequences by BLAST and searching for apparent frameshifts. When frameshifts were identified by this analysis, the sequence assembly was consulted for evidence of sequencing errors and if found, they were corrected. The sequences were also searched for any that could extend the 5' end of the sequence and these were incorporated when found. High quality sequence discrepancies between different sequence reads were identified and resolved. Sequence reads classified as deleted or chimeric were identified through manual inspection and removed from the assembly. The resulting sequence has an average PHRED consensus quality score of 89.96. The lowest quality bases in the assembly are in the immediate vicinity of the 5' and 3' ends of the viral genome, with the lowest quality base having a PHRED score of 35. Most (29,694 of the 29,736 (99.86%)) of the bases have a consensus score of 90. Almost all regions of the genome are represented by reads derived from both strands of the plasmid sequencing templates, the exceptions being 50 bases at the 5' end represented by a single sequencing read, and 5 bases at the 3' end

represented by a single read. The average base in the assembly is represented by 30 reads in the forward direction and 30 reads in the reverse direction, as determined by PHRED. RT-PCR products predicted from the sequence and spanning the entire genome yield PCR products of the anticipated size on agarose gels. To confirm the 5' end of the viral genome RACE was performed using the RLM-RACE kit from Ambion, and primers 5'-CAGGAAACAGCTATGACACCAAGAACAAGGCTCTCCA-3' (SEQ ID NO: 90) and 5'-CAGGAAACAGCTATGACGATAGGGCCTCTTCCACAGA-3' (SEQ ID NO: 91). Fourteen clones were recovered and sequenced. Analysis of these sequences confirmed the 5' end of the coronavirus genome. The SARS genomic sequences have been deposited into Genbank (Accession Nos. AY274119.1, AY274119.2, and AY274119.3).

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While the invention has been described in connection with specific

embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains, and may be applied to the essential features set forth herein and in the scope of the appended claims.

All patents, patent applications, and publications referred to herein are hereby incorporated by reference in their entirety to the same extent as if each individual patent, patent application, or publication was specifically and individually indicated to be incorporated by reference in its entirety.

# What is claimed is:

- 1. A substantially pure SARS virus nucleic acid molecule.
- 5 2. The molecule of claim 1, wherein said molecule is selected from the group consisting of genomic RNA or DNA, cDNA, synthetic DNA, or mRNA.
  - 3. The molecule of claim 1 or 2, wherein said molecule comprises a sequence substantially identical to a sequence selected from the group consisting of SEQ ID NOs: 1-13, 15-18, 20-30, 90-159, 208, and 209 or a fragment thereof.
  - 4. The molecule of claim 3, wherein said molecule comprises a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO:2, and SEQ ID NO: 15 or a fragment thereof.

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- 5. The molecule of claim 3, wherein said molecule comprises a sequence substantially identical to a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 15, or a fragment thereof.
- 20 6. The molecule of any one of claims 1 through 3, wherein said molecule comprises a s2m motif.
  - 7. The molecule of claim 6, wherein said s2m motif comprises a sequence substantially identical to a sequence selected from the group consisting of SEQ ID NOs: 16, 17, and 18.
  - 8. The molecule of any one of claims 1 through 3, wherein said molecule comprises a leader sequence.
- 30 9. The molecule of claim 8, wherein said leader sequence comprises a sequence substantially identical to the sequence of SEQ ID NO: 3.

- 10. The molecule of any one of claims 1 through 3, wherein said molecule comprises a transcriptional regulatory sequence.
- The molecule of claim 10, wherein said transcriptional regulatory sequence
   comprises a sequence substantially identical to the sequence selected from the group consisting of SEQ ID NOs: 4-13 and 20-30.
- 12. The molecule of claim 1, wherein said molecule comprises a sequence substantially identical to a sequence selected from nucleotides 265-13,398; 13,398-21,485; 21,492 25,259; 25,268 26,092; 25,689 26,153; 26,117 26,347; 26,398 27,063; 27,074 27,265; 27,273 27,641; 27,638 27,772; 27,779 27,898; 27,864 28,118; 28,120 29,388; 28,130 28,426; 28,583 28,795; and 29,590 29,621 of SEQ ID NO: 15.
- 15 13. The molecule of any one of claims 1 through 3, wherein said molecule encodes a polyprotein.
  - 14. The molecule of any one of claims 1 through 3, wherein said molecule encodes a polypeptide.

- 15. A substantially pure SARS virus polypeptide.
- 16. The polypeptide of claim 15, wherein said polypeptide comprises a polyprotein.

- 17. The polypeptide of claim 15, wherein said polypeptide comprises an identifiable signal sequence.
- 18. The polypeptide of claim 17, wherein said signal sequence comprises a30 sequence substantially identical to a sequence selected from the group consisting of SEQ ID NOs: 76 and 85.

- 19. The polypeptide of claim 15, wherein said polypeptide comprises a transmembrane domain.
- The polypeptide of claim 19, wherein said transmembrane domain comprises a
   sequence substantially identical to a sequence selected from the group consisting of
   SEQ ID NOs: 77-86.
  - 21. The polypeptide of claim 15, wherein said polypeptide comprises a glycoprotein.

- 22. The polypeptide of claim 21, wherein said glycoprotein comprises a matrix glycoprotein.
- 23. The polypeptide of claim 22, wherein said matrix glycoprotein comprises asequence substantially identical to SEQ ID NO: 34.
  - 24. The polypeptide of claim 15, wherein said polypeptide is selected from the group consisting of a transmembrane protein and a multitransmembrane protein.
- 25. The polypeptide of claim 15, wherein said polypeptide is selected from the group consisting of a type I transmembrane protein and a type II transmembrane protein.
- 26. The polypeptide of claim 24, wherein said polypeptide comprises a25 transmembrane anchor or a a transmembrane helix.
  - 27. The polypeptide of any one of claims 1 through 3, wherein said polypeptide comprises an epitope of a SARS virus
- 28. The polypeptide of claim 15, wherein said polypeptide comprises an ATP-30 binding domain.

- 29. The polypeptide of claim 15, wherein said polypeptide comprises a viral envelope protein.
- 30. The polypeptide of claim 15, wherein said polypeptide comprises a nuclear 5 localization signal.
  - 31. The polypeptide of claim 15, wherein said polypeptide comprises a lysine-rich sequence.
- 10 32. The polypeptide of claim 31, wherein said lysine-rich sequence comprises a sequence substantially identical to SEQ ID NO: 14.
  - The polypeptide of claim 15, wherein said polypeptide comprises a RNA binding protein.

- 34. The polypeptide of claim 15, wherein said polypeptide comprises a hydrophilic domain.
- 35. The polypeptide of claim 34, wherein said hydrophilic domain comprises a sequence substantially identical to SEQ ID NO: 87.
  - 36. The polypeptide of claim 15, wherein said polypeptide is selected from the group consisting of replicase 1a, replicase 1b, spike glycoprotein, small envelope protein, matrix glycoprotein, and nucleocapsid protein.

- 37. The polypeptide of claim 15, wherein said polypeptide comprises a sequence substantially identical to a sequence selected from the group consisting of SEQ ID NOs: 14, 33-36, 64-74, and 76-87 or a fragment thereof.
- 30 38. A vector comprising the nucleic acid molecule of claim 1.

- 39. The vector of claim 38, wherein said vector comprises a sequence substantially identical to a sequence selected from the group consisting of SEQ ID NOs: 1-13, 15-18, 20-30, 90-159, 208, and 209.
- 5 40. The vector of claim 38, wherein said vector is a gene therapy vector.
  - 41. A host cell comprising the vector of claim 38.
- 42. The host cell of claim 41, wherein said cell is selected from the group consisting of a mammalian cell, a yeast, a bacterium, and a nematode cell.
- 43. A nucleic acid molecule having substantial nucleotide sequence identity to a sequence encoding a SARS virus polypeptide or fragment thereof, wherein said fragment comprises at least six amino acids, and wherein said nucleic acid molecule
   15 hybridizes under high stringency conditions to at least a portion of a SARS virus nucleic acid molecule.
- 44. The nucleic acid molecule of claim 43, wherein said nucleic acid molecule has
   100% sequence complementarity to said sequence encoding a SARS virus polypeptide
   20 or fragment thereof.
  - 45. A nucleic acid molecule having substantial nucleotide sequence identity to a SARS virus nucleotide sequence, wherein said nucleic acid molecule comprises at least ten nucleotides, and wherein said nucleic acid molecule hybridizes under high stringency conditions to at least a portion of a SARS virus nucleic acid molecule.
  - 46. The nucleic acid molecule of claim 45, wherein said nucleic acid molecule has 100% sequence complementarity to said SARS virus nucleotide sequence.
- 30 47. A nucleic acid molecule comprising a sequence that is antisense to a SARS virus nucleic acid molecule

- 48. An antibody that specifically binds to a SARS virus polypeptide.
- 49. The antibody of claim 48, wherein said antibody is a neutralizing antibody.
- 5 50. A method for detecting a SARS virus virion or polypeptide in a sample, said method comprising contacting said sample with the antibody of claim 48, and determining whether said antibody specifically binds to said polypeptide.
- 51. A method for detecting a SARS virus genome or gene or homolog or fragment thereof in a sample, said method comprising contacting a SARS virus nucleic acid molecule, wherein said nucleic acid molecule comprises at least ten nucleotides, with a preparation of DNA from said sample, under hybridization conditions providing detection of DNA sequences having nucleotide sequence identity to a SARS virus nucleic acid molecule.

52. The method of claim 31, wherein said nucleic acid molecule comprises at least one of a primer pair, wherein said primer pair hybridizes to said a SARS virus genome or gene or homolog or fragment thereof under conditions suitable for polymerase chain reaction.

- 53. A method of targeting a protein for secretion from a cell, said method comprising attaching a signal sequence from a SARS virus polypeptide to said protein, such that said protein is secreted from said cell.
- 25 54. A nucleic acid molecule comprising a sequence complementary to a SARS virus nucleotide sequence.
- 55. A kit for detecting the presence of a SARS virus nucleic acid molecule or polypeptide in a sample, said kit comprising a reagent selected from the group
   30 consisting of a SARS virus nucleic acid molecule and an antibody that specifically binds a SARS virus polypeptide.

- 56. A method for eliciting an immune response in an animal, said method comprising identifying an animal infected with or at risk for infection with a SARS virus, and administering a SARS virus polypeptide or fragment thereof, or administering a SARS virus nucleic acid molecule encoding a SARS virus polypeptide or fragment thereof, to said animal.
- 57. The method of claim 56, wherein said administering results in the production of an antibody in said animal.
- 10 58. The method of claim 56, wherein said administering results in the generation of cytotoxic or helper T-lymphocytes in said animal.
- 59. A method for treating or preventing a SARS virus infection comprising identifying an animal infected with or at risk for infection with a SARS virus, and
   15 administering a SARS virus nucleic acid molecule or polypeptide, or administering a compound that inhibits pathogenicity or replication of a SARS virus, to the animal.
  - 60. The method of claim 59, wherein the animal is a human.
- 20 61. Use of a SARS virus nucleic acid molecule or polypeptide for treating or preventing a SARS virus infection.
- 62. A method of identifying a compound for treating or preventing a SARS virus infection, comprising contacting sample comprising a SARS virus nucleic acid
   25 molecule or contacting a SARS virus polypeptide with the compound, wherein an increase or decrease in the expression or activity of the nucleic acid molecule or the polypeptide identifies a compound for treating or preventing a SARS virus infection.
  - 63. A vaccine comprising a SARS virus nucleic acid molecule or polypeptide.
  - 64. The vaccine of claim 62, wherein the vaccine is a DNA vaccine.

65. A microarray comprising a plurality of elements, wherein each element comprises one or more distinct nucleic acid or amino acid sequences, and wherein the sequences are selected from a SARS virus nucleic acid molecule or polypeptide, or a antibody that specifically binds a SARS virus nucleic acid molecule or polypeptide.

- 66. A computer readable record comprising distinct SARS virus nucleic acid or amino acid sequences.
- 67. The computer readable record of claim 65, wherein the computer readable record comprises a database.

PCT/CA2004/000626

# Replicase 1A

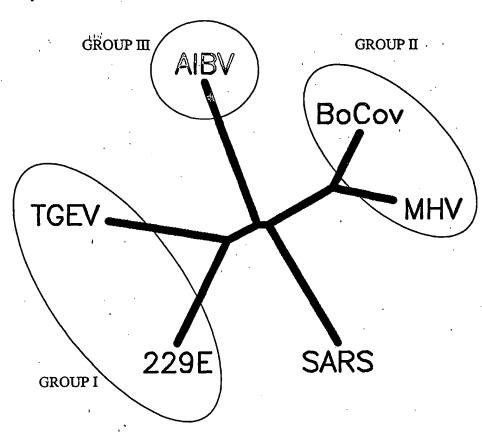


Figure 1A

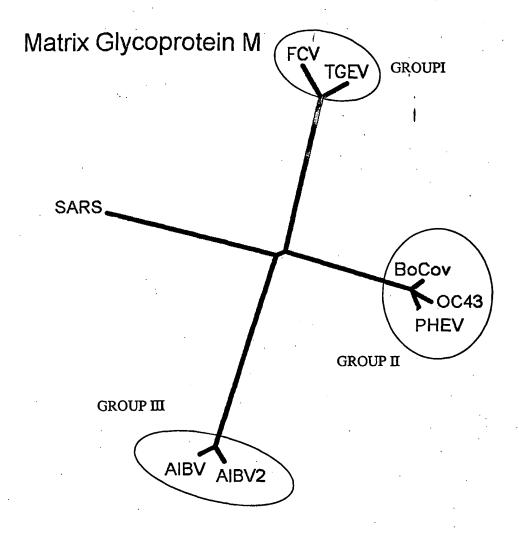


Figure 1B

# Nucleocapsid

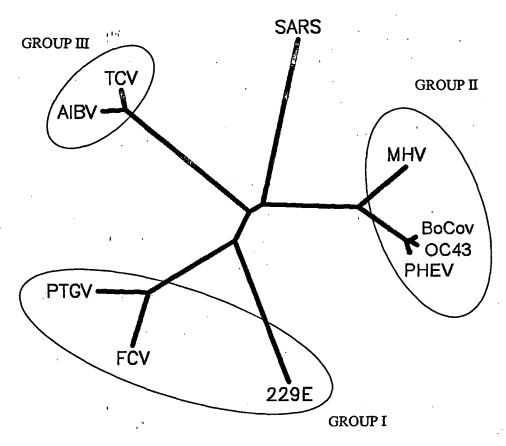


Figure 1C

# S (Spike) Glycoprotein

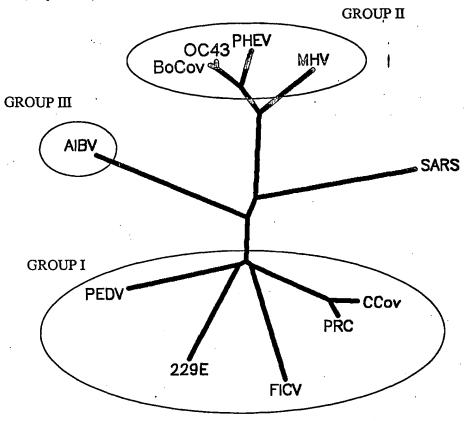


Figure 1D

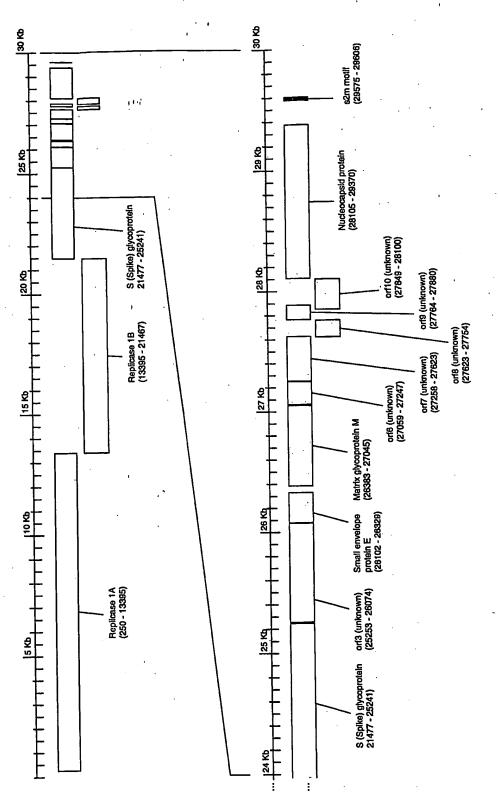


Figure 2

CTACCCAGGAAAAGCCAACCAACCTCGATCTCTTGTAGATCTGTTCTCTAAACGAACTTTAAAATCTGTGT AGCTGTCGCTCGGCTGCATGCCTAGTGCACCTACGCAGTATAAACAATAATAAATTTTACTGTCGTTGACA AGAAACGAGTAACTCGTCCCTCTTCTGCAGACTGCTTACGGTTTCGTCCGTGTTGCAGTCGATCATCAGCA TACCTAGGTTTCGTCCGGGTGTGACCGAAAGGTAAGATGGAGAGCCTTGTTCTTGGTGTCAACGAGAAAAC ACACGTCCAACTCAGTTTGCCTGTCCTTCAGGTTAGAGACGTGCTAGTGCGTGGCTTCGGGGACTCTGTGG AAGAGGCCCTATCGGAGGCACGTGAACACCTCAAAAATGGCACTTGTGGTCTAGTAGAGCTGGAAAAAAGGC GTACTGCCCCAGCTTGAACAGCCCTATGTGTTCATTAAACGTTCTGATGCCTTAAGCACCAATCACGGCCA CAAGGTCGTTGAGCTGGTTGCAGAAATGGACGGCATTCAGTACGGTCGTAGCGGTAFAACACTGGGAGTAC TCGTGCCACATGTGGGCGAAACCCCAATTGCATACCGCAATGTTCTTCTTCGTAAGAACGGTAATAAGGGA GCCGGTGGTCATAGCTATGGCATCGATCTAAAGTCTTATGACTTAGGTGACGAGCTTGGCACTGATCCCAT ATGGAGGTGCAGTCACTCGCTATGTCGACAACAATTTCTGTGGCCCAGATGGGTACCCTCTTGATTGCATC AAAGATTTTCTCGCACGCGCGGCAAGTCAATGTGCACTCTTTCCGAACAACTTGATTACATCGAGTCGAA GAGAGGTGTCTACTGCTGCCGTGACCATGAGCATGAAATTGCCTGGTTCACTGAGCGCTCTGATAAGAGCT ACGAGCACCAGACACCCTTCGAAATTAAGAGTGCCAAGAAATTTGACACTTTCAAAGGGGGAATGCCCAAAG TTTGTGTTTCCTCTTAACTCAAAAGTCAAAGTCATCAACCACGTGTTGAAAAAGAAAAAAGACTGAGGGTTT CATGGGGCGTATACGCTCTGTGTACCCTGTTGCATCTCCACAGGAGTGTAACAATATGCACTTGTCTACCT TGATGAAATGTAATCATTGCGATGAAGTTTCATGGCAGACGTGCGACTTTCTGAAAGCCACTTGTGAACAT TGTGGCACTGAAAATTTAGTTATTGAAGGACCTACTACATGTGGGTACCTACTACTAATGCTGTAGTGAA **AATGCCATGTCCTGCCTGTCAAGACCCAGAGATTGGACCTGAGCATAGTGTTGCAGATTATCACAACCACT** CAAACATTGAAACTCGACTCCGCAAGGGAGGTAGGACTAGATGTTTTGGAGGCTGTGTGTTTGCCTATGTT GGCTGCTATAATAAGCGTGCCTACTGGGTTCCTCGTGCTAGTGCTGATATTGGCTCAGGCCATACTGGCAT TACTGGTGACAATGTGGAGACCTTGAATGAGGATCTCCTTGAGATACTGAGTCGTGAACGTGTTAACATTA ACATTGTTGGCGATTTTCATTTGAATGAAGAGGTTGCCATCATTTTGGCATCTTTCTCTGCTTCTACAAGT GCCTTTATTGACACTATAAAGAGTCTTGATTACAAGTCTTTCAAAAACCATTGTTGAGTCCTGCGGTAACTA TAAAGTTACCAAGGGAAAGCCCGTAAAAGGTGCTTGGAACATTGGACAACAGAGATCAGTTTTAACACCAC TGTGTGGTTTTCCCTCACAGGCTGCTGGTGTTATCAGATCAATTTTTGCGCGCACACTTGATGCAGCAAAC CACTCAATTCCTGATTTGCAAAGAGCAGCTGTCACCATACTTGATGGTATTTCTGAACAGTCATTACGTCT TGTCGACGCCATGGTTTATACTTCAGACCTGCTCACCAACAGTGTCATTATTATGGCATATGTAACTGGTG GTCTTGTACAACAGACTTCTCAGTGGTTGTCTAATCTTTTGGGCACTACTGTTGAAAAACTCAGGCCTATC TTTGAATGGATTGAGGCGAAACTTAGTGCAGGAGTTGAATTTCTCAAGGATGCTTGGGAGATTCTCAAATT  ${\tt TCTCATTACAGGTGTTTTTGACATCGTCAAGGGTCAAATACAGGTTGCTTCAGATAACATCAAGGATTGTG}$ TAAAATGCTTCATTGATGTTGATCAAGGCACTCGAAATGTGCATTGATCAAGTCACTATCGCTGGCGCA AAGTTGCGATCACTCAACTTAGGTGAAGTCTTCATCGCTCAAAGCAAGGGACTTTACCGTCAGTGTATACG TGGCAAGGAGCAGCTGCAACTACTCATGCCTCTTAAGGCACCAAAAGAAGTAACCTTTCTTGAAGGTGATT CACATGACACAGTACTTACCTCTGAGGAGGTTGTTCTCAAGAACGGTGAACTCGAAGCACTCGAGACGCCC GTTGATAGCTTCACAAATGGAGCTATCGTCGGCACACCAGTCTGTGTAAATGGCCTCATGCTCTTAGAGAT GGGGTGCACCAATTAAAGGTGTAACCTTTGGAGAAGATACTGTTTGGGAAGTTCAAGGTTACAAGAATGTG AGAATCACATTTGAGCTTGATGAACGTGTTGACAAAGTGCTTAATGAAAAGTGCTCTGTCTACACTGTTGA ATCCGGTACCGAAGTTACTGAGTTTGCATGTGTTGTAGCAGAGGCTGTTGTGAAGACTTTACAACCAGTTT CTGATCTCCTTACCAACATGGGTATTGATCTTGATGAGGTGGAGTGTAGCTACATTCTACTTATTTGATGAT GCTGGTGAAGAAACTTTTCATCACGTATGTATTGTTCCTTTTACCCTCCAGATGAGGAAGAAGAGACGACGA TGCAGAGTGTGAGGAAGAAGAATTGATGAAACCTGTGAACATGAGTACGGTACAGAGGATGATTATCAAG GTCTCCCTCTGGAATTTGGTGCCTCAGCTGAAACAGTTCGAGTTGAGGAAGAAGAAGAAGAAGAAGACTGGCTG GATGATACTACTGAGCAATCAGAGATTGAGCCAGAACCAGAACCTACACCTGAAGAACCAGTTAATCAGTT TACTGGTTATTTAAAACTTACTGACAATGTTGCCATTAAATGTGTTGACATCGTTAAGGAGGCACAAAGTG CTAATCCTATGGTGATTGTAAATGCTGCTAACATACACCTGAAACATGGTGGTGGTGGTAGCAGGTGCACTC AACAAGGCAACCAATGGTGCCATGCAAAAGGAGAGTGATGATTACATTAAGCTAAATGGCCCTCTTACAGT AGGAGGGTCTTGTTTGCTTTCTGGACATAATCTTGCTAAGAAGTGTCTGCATGTTGTTGGACCTAACCTAA ATGCAGGTGAGGACATCCAGCTTCTTAAGGCAGCATATGAAAATTTCAATTCACAGGACATCTTACTTGCA TACACAGGTTTATATTGCAGTCAATGACAAAGCTCTTTATGAGCAGGTTGTCATGGATTATCTTGATAACC TGAAGCCTAGAGTGGAAGCACCTAAACAAGAGGAGCCACCAAACACAGAAGATTCCAAAACTGAGGAGAAA TCTGTCGTACAGAAGCCTGTCGATGTGAAGCCAAAAATTAAGGCCTGCATTGATGAGGTTACCACAACACT GGAAGAAACTAAGTTTCTTACCAATAAGTTACTCTTGTTTGCTGATATCAATGGTAAGCTTTACCATGATT CTCAGAACATGCTTAGAGGTGAAGATATGTCTTTCCTTGAGAAGGATGCACCTTACATGGTAGGTGATGTT

ATCACTAGTGGTGATATCACTTGTGTTGTAATACCCTCCAAAAAGGCTGGTGGCACTACTGAGATGCTCTC AAGAGCTTTGAAGAAAGTGCCAGTTGATGAGTATATAACCACGTACCCTGGACAAGGATGTGCTGGTTATA CACTTGAGGAAGCTAAGACTGCTCTTAAGAAATGCAAATCTGCATTTTATGTACTACCTTCAGAAGCACCT AAGAAAATTAATGCCTATATGCATGGATGTTAGAGCCATAATGGCAACCATCCAACGTAAGTATAAAGGAA TTAAAATTCAAGAGGGCATCGTTGACTATGGTGTCCGATTCTTCTTTTATACTAGTAAAGAGCCTGTAGCT TCTATTATTACGAAGCTGAACTCTCTAAATGAGCCGCTTGTCACAATGCCAATTGGTTATGTGACACATGG TTTTAATCTTGAAGAGGCTGCGCCTGTATGCGTTCTCTTAAAGCTCCTGCCGTAGTGTCAGTATCATCAC CAGATGCTGTTACTACATATAATGGATACCTCACTTCGTCATCAAAGACATCTGAGGAGCACTTTGTAGAA ACAGTTTCTTTGGCTGGCTCTTACAGAGATTGGTCCTATTCAGGACAGCGTACAGAGTTAGGTGTTGAATT TCTTAAGCGTGGTGACAAAATTGTGTACCACACTCTGGAGAGCCCCGTCGAGTTTCATCTTGACGGTGAGG TTCTTTCACTTGACAAACTAAAGAGTCTCTTATCCCTGCGGGAGGTTAAGACTATAAAAGTGTTCACAACT GTGGACAACACTAATCTCCACACACACGCTTGTGGATATGTCTATGACATATGGACAGCAGTTTGGTCCAAC TACCTAGTGATGACACACTACGTAGTGAAGCTTTCGAGTACTACCATACTCTTGATGAGAGTTTTCTTGGT AGGTACATGTCTGCTTTAAACCACAAAGAAATGGAAATTTCCTCAAGTTGGTGGTTTAACTTCAATTAA ATGGGCTGATAACAATTGTTATTTGTCTAGTGTTTTTATTAGCACTTCAACAGCTTGAAGTCAAATTCAATG CACCAGCACTTCAAGAGGCTTATTATAGAGCCCGTGCTGGTGATGCTGCTAACTTTTGTGCACTCATACTC GCTTACAGTAATAAAACTGTTGGCGAGCTTGGTGATGTCAGAGAAACTATGACCCATCTTCTACAGCATGC TAATTTGGAATCTGCAAAGCGAGTTCTTAATGTGGTGTGTAAACATTGTGGTCAGAAAACTACTACCTTAA  ${\tt CGGGTGTAGAAGCTGTGATGTATATGGGTACTCTATCTTATGATAATCTTAAGACAGGTGTTTCCATTCATTCCATTCCATTCCATTCCATTCCATTCCATTCCATTCCAT$ TGTGTGTGTGTGTGTGATGCTACACAATATCTAGTACAACAAGAGTCTTCTTTTGTTATGATGTCTGCACC ACCTGCTGAGTATAAATTACAGCAAGGTACATTCTTATGTGCGAATGAGTACACTGGTAACTATCAGTGTG GTCATTACACTCATATAACTGCTAAGGAGACCCTCTATCGTATTGACGGAGCTCACCTTACAAAGATGTCA GAGTACAAAGGACCAGTGACTGATGTTTTCTACAAGGAAACATCTTACACTACAACCATCAAGCCTGTGTC GTATAAACTCGATGGAGTTACTTACACAGAGATTGAACCAAAATTGGATGGGTATTATAAAAAGGATAATG CTTACTATACAGAGCAGCCTATAGACCTTGTACCAACTCAACCATTACCAAATGCGAGTTTTGATAATTTC AAACTCACATGTTCTAACACAAAATTTGCTGATGATTTAAATCAAATGACAGGCTTCACAAAGCCAGCTTC ACGAGAGCTATCTGTCACATTCTTCCCAGACTTGAATGGCGATGTAGTGGCTATTGACTATAGACACTATT CAGCGAGTTTCAAGAAAGGTGCTAAATTACTGCATAAGCCAATTGTTTGGCACATTAACCAGGCTACAACC AAGACAACGTTCAAACCAAACACTTGGTGTTTACGTTGTCTTTGGAGTACAAAGCCAGTAGATACTTCAAA GTTGTAGGCAATGTCATACTTAAACCATCAGATGAAGGTGTTAAAGTAACACAAGAGTTAGGTCATGAGGA TCTTATGGCTGCTTATGTGGAAAACACAAGCATTACCATTAAGAAACCTAATGAGCTTTCACTAGCCTTAG GTTTAAAAACAATTGCCACTCATGGTATTGCTGCAATTAATAGTGTTCCTTGGAGTAAAATTTTTGGCTTAT GTCAAACCATTCTTAGGACAAGCAGCAATTACAACATCAAATTGCGCTAAGAGATTAGCACAACGTGTGTT TAACAATTATATGCCTTATGTGTTTACATTATTGTTCCAATTGTGTACTTTACTAAAAGTACCAATTCTA GAATTAGAGCTTCACTACCTACAACTATTGCTAAAAATAGTGTTAAGAGTGTTGCTAAATTATGTTTGGAT GCCGGCATTAATTATGTGAAGTCACCCAAATTTTCTAAATTGTTCACAATCGCTATGTGGCTATTGTTGTT AAGTATTTGCTTAGGTTCTCTAATCTGTGTAACTGCTGCTTTTTGGTGTACTCTTATCTAATTTTGGTGCTC CTTCTTATTGTAATGGCGTTAGAGAATTGTATCTTAATTCGTCTAACGTTACTACTATGGATTTCTGTGAA GGTTCTTTTCCTTGCAGCATTTGTTTAAGTGGATTAGACTCCCTTGATTCTTATCCAGCTCTTGAAACCAT TCAGGTGACGATTTCATCGTACAAGCTAGACTTGACAATTTTAGGTCTGGCCGCTGAGTGGGTTTTGGCAT GCTAGTCATTCATCAGCAATTCTTGGCTCATGTGGTTTATCATTAGTATTGTACAAATGGCACCCGTTTC TGCAATGGTTAGGATGTACATCTTCTTTGCTTCTTTCTACTACATATGGAAGAGCTATGTTCATATCATGG ATGGTTGCACCTCTTCGACTTGCATGATGTGCTATAAGCGCAATCGTGCCACACGCGTTGAGTGTACAACT ATTGTTAATGGCATGAAGAGATCTTTCTATGTCTATGCAAATGGAGGCCGTGGCTTCTGCAAGACTCACAA TGTCACTCCAGTTTAAAAGACCAATCAACCCTACTGACCAGTCATCGTATATTGTTGATAGTGTTGCTGTG AAAAATGGCGCGCTTCACCTCTACTTTGACAAGGCTGGTCAAAAGACCTATGAGAGACATCCGCTCTCCCA TTTTGTCAATTTAGACAATTTGAGAGCTAACAACACTAAAGGTTCACTGCCTATTAATGTCATAGTTTTTG ATGGCAAGTCCAAATGCGACGAGTCTGCTTCTAAGTCTGCTTCTGTGTACTACAGTCAGCTGATGTGCCAA CCTATTCTGTTGCTTGACCAAGCTCTTGTATCAGACGTTGGAGATAGTACTGAAGTTTCCGTTAAGATGTT TGATGCTTATGTCGACACCTTTTCAGCAACCTTTTAGTGTTCCTATGGAAAAACTTAAGGCACTTGTTGCTA CAGCTCACAGCGAGTTAGCAAAGGGTGTAGCTTTAGATGGTGTCCTTTCTACATTCGTGTCAGCTGCCCGA CAAGGTGTTGTTGATACCGATGTTGACACAAAGGATGTTATTGAATGTCTCAAACTTTCACATCACTCTGA CTTAGAAGTGACAGGTGACAGTTGTAACAATTTCATGCTCACCTATAATAAGGTTGAAAACATGACGCCCA GAGATCTTGGCGCATGTATTGACTGTAATGCAAGGCATATCAATGCCCAAGTAGCAAAAAGTCACAATGTT TCACTCATCTGGAATGTAAAAGACTACATGTCTTTATCTGAACAGCTGCGTAAACAAATTCGTAGTGCTGC CAAGAAGAACAACATACCTTTTAGACTAACTTGTGCTACAACTAGACAGGTTGTCAATGTCATAACTACTA AAATCTCACTCAAGGGTGGTAAGATTGTTAGTACTTGTTTTAAACTTATGCTTAAGGCCACATTATTGTGC TGAAATCATTGGTTACAAAGCCATTCAGGATGGTGTCACTCGTGACATCATTTCTAÇTGATGATT**GTTTTG** CAAATAAACATGCTGGTTTTGACGCATGGTTTAGCCAGCGTGGTGGTTCATACAAAAATGACAAAAAGCTGC CCTGTAGTAGCTGCTATCATTACAAGAGAGATTGGTTTCATAGTGCCTGGCTTACCGGGTACTGT**GCTGAG** AGCAATCAATGGTGACTTCTTGCATTTTCTACCTCGTGTTTTTAGTGCTGTTGGCAACATTTGCTACACAC CTTCCAAACTCATTGAGTATAGTGATTTTGCTACCTCTGCTTGCGTTCTTGCTGCTGAGTGTACAATTTTT TGAGCTTCGTCCAGACACTCGTTATGTGCTTATGGATGGTTCCATCATACAGTTTCCTAACACTTACCTGG AGGGTTCTGTTAGAGTAGTAACAACTTTTGATGCTGAGTACTGTAGACATGGTACATGCGAAAGGTCAGAA GTAGGTATTTGCCTATCTACCAGTGGTAGATGGGTTCTTAATAATGAGCATTACAGAGCTCTATCAGGAGT TTTCTGTGGTGTTGATGCGATGAATCTCATAGCTAACATCTTTACTCCTCTTGTGCAACCTGTGGGTGCTT TAGATGTGTCTGCTTCAGTAGTGGCTGGTGGTATTATTGCCATATTGGTGACTTGTGCTGCCTACTACTTT ATGAAATTCAGACGTGTTTTTGGTGAGTACAACCATGTTGTTGCTGCTAATGCACTTTTGTTTTTGATGTC TTTCACTATACTCTGTCTGGTACCAGCTTACAGCTTTCTGCCGGGAGTCTACTCAGTCTTTTACTTGTACT TGACATTCTATTTCACCAATGATGTTTCATTCTTGGCTCACCTTCAATGGTTTGCCATGTTTTCTCCTATT GTGCCTTTTTGGATAACAGCAATCTATGTATTCTGTATTTCTCTGAAGCACTGCCATTGGTTCTTTAACAA TTTTGCTCAACAAGGAAATGTACCTAAAATTGCGTAGCGAGACACTGTTGCCACTTACACAGTATAACAGG TATCTTGCTCTATATAACAAGTACAAGTATTTCAGTGGAGCCTTAGATACTACCAGCTATCGTGAAGCAGC AGACATCAATCACTTCTGCTGTTCTGCAGAGTGGTTTTAGGAAAATGGCATTCCCGTCAGGCAAAGTTGAA GGGTGCATGGTACAAGTAACCTGTGGAACTACAACTCTTAATGGATTGTGGTTGGATGACACAGTATACTG TCCAAGACATGTCATTTGCACAGCAGAAGACATGCTTAATCCTAACTATGAAGATCTGCTCATTCGCAAAT  $\tt CCAACCATAGCTTTCTTGTTCAGGCTGGCAATGTTCAACTTCGTGTTATTGGCCATTCTATGCAAAATTGTTCAACTTCGTGTTATTGGCCATTCTATGCAAAATTGTTCAACTTCGTGTTATTGGCCATTCTATTGCAAAATTGTTCAACTTCGTGTTATTGGCCATTCTATTGCAAAATTGTTCAACTTCGTGTTATTGGCCATTCTATTGCAAAATTGTTCAACTTCGTGTTATTGGCCATTCTATTGCAAAAATTGTTCAACTTCGTGTTATTGGCCATTCTATTGCAAAAATTGTTCAACTTCGTGTTATTGGCCATTCTATTGCAAAAATTGTTCAACTTCGTGTTATTGGCCAATGTTCAACTTCGTGTTATTGGCCAAAAATTGTTCAACTTCGTGTTATTGGCCAATGTTCAACTTCGTGTTATTGGCCAAAAATTGTTCAACTTCGTGTTATTGGCCAAAAATTGTTCAACTTCGTGTTATTGGCCAAAAATTGTTCAACTTCGTGTTATTGGCCAAAAATTGTTCAACTTCGTGTTATTGGCCAAAAATTGTTCAACTTCGTGTTATTGGCCAAAAATTGTTCAACTTCGTGTTATTGGCCAAAAATTGTTCAACTTCGTGTTATTGGCCAAAAAATTGTTCAACTTCGTGTTATTGGCCAAAAAATTGTTCAACTTCGTGTTATTGGCCAAAAAATTGTTCAACTTCGTGTTATTGGCAAAAAATTGTTCAACTTCGTGTTATTGGCCAAAAAATTGTTCAACTTCGTGTTATTGGCCAAAAAATTGTTCAACTTCGTGTTATTGGCCAATGTTCAACTTGTTATTGGCCAAAAAATTGTTCAACTTCAACTTCAACTTTCAACTTTCAACTTCAACTTTCAACTTCAACTTTCAACTTTCAACTTTCAACTTTCAACTTTCAACTTTCAACTTTCAACTTTCAACTTTCAACTTTCAACTTTCAACTTCAACTTTCAACTTTCAACTTTCAACTTCAACTTTCAACTTCAACTTCAACTTCAACTTCAACTTCAACTTCAACTTCAACTTCAACTTCAACTTTCAACTTTCAACTTCAACTTCAACTTCAACTTCAACTTCAACTTCAACTTCA$  $\tt CTGCTTAGGCTTAAAGTTGATACTTCTAACCCTAAGACACCCAAGTATAAATTTGTCCGTATCCAACCTGG$ TCAAACATTTTCAGTTCTAGCATGCTACAATGGTTCACCATCTGGTGTTTATCAGTGTGCCATGAGACCTA ATCATACCATTAAAGGTTCTTTCCTTAATGGATCATGTGGTAGTGTTGGTTTTAACATTGATTATGATTGC GTGTCTTTCTGCTATATGCATCATATGGAGCTTCCAACAGGAGTACACGCTGGTACTGACTTAGAAGGTAA ATTCTATGGTCCATTTGTTGACAGACAAACTGCACAGGCTGCAGGTACAGACAACCATAACATTAAATG TTTTGGCATGGCTGTATGCTGCTGTTATCAATGGTGATAGGTGGTTTCTTAATAGATTCACCACTACTTTG AATGACTTTAACCTTGTGGCAATGAAGTACAACTATGAACCTTTGACACAAGATCATGTTGACATATTGGG ACCTCTTTCTGCTCAAACAGGAATTGCCGTCTTAGATATGTGTGCTGCTTTGAAAGAGCTGCTGCAGAATG **AACTTTCTTGACATCACTATTGATTCTTGTTCAAAGTACACAGTGGTCACTGTTTTTCTTTGTTTACGAGA** ATGCTTTCTTGCCATTTACTCTTGGTATTATGGCAATTGCTGCATGTGCTATGCTGCTTGTTAAGCATAAG CACGCATTCTTGTGCTTGTTTCTGTTACCTTCTCTTGCAACAGTTGCTTACTTTAATATGGTCTACATGCC TGCTAGCTGGGTGATGCGTATCATGACATGGCTTGAATTGGCTGACACTAGCTTGTCTGGTTATAGGCTTA AGGATTGTGTTATGTATGCTTCAGCTTTAGTTTTGCTTATTCTCATGACAGCTCGCACTGTTTATGATGAT  ${\tt GCTGCTAGACGTGTTTGGACACTGATGAATGTCATTACACTTGTTTACAAAGTCTACTATGGTAATGCTTT}$ AGATCAAGCTATTTCCATGTGGGCCTTAGTTATTTCTGTAACCTCTAACTATTCTGGTGTCGTTACGACTA ACCTTACAGTGTATCATGCTTTATTGTTTCTTAGGCTATTGTTGCTGCTGCTACTTTGGCCTTTTCTG ATATGAACTCCCAGGGGCTTTTGCCTCCTAAGAGTAGTATTGATGCTTTCAAGCTTAACATTAAGTTGTTG GGTATTGGAGGTAAACCATGTATCAAGGTTGCTACTGTACAGTCTAAAATGTCTGACGTAAAGTGCACATC TGTGGTACTGCTCTCGGTTCTTCAACAACTTAGAGTAGAGTCATCTTCTAAATTGTGGGCACAATGTGTAC AACTCCACAATGATATTCTTCTTGCAAAAGACACAACTGAAGCTTTCGAGAAGATGGTTTCTCTTTTGTCT GTTTTGCTATCCATGCAGGGTGCTGTAGACATTAATAGGTTGTGCGAGGAAATGCTCGATAACCGTGCTAC TCTTCAGGCTATTGCTTCAGAATTTAGTTCTTTACCATCATATGCCGCTTATGCCACTGCCCAGGAGGCCT ATGAGCAGGCTGTAGCTAATGGTGATTCTGAAGTCGTTCTCAAAAAGTTAAAGAAATCTTTGAATGTGGCT AAATCTGAGTTTGACCGTGATGCTGCCATGCAACGCAAGTTGGAAAAGATGGCAGATCAGGCTATGACCCA AATGTACAAACAGGCAAGATCTGAGGACAAGAGGGCAAAAGTAACTAGTGCTATGCAAACAATGCTCTTCA CTATGCTTAGGAAGCTTGATAATGATGCACTTAACAACATTATCAACAATGCGCGTGATGGTTGTTCCA CTCAACATCATACCATTGACTACAGCAGCCAAACTCATGGTTGTTGTCCCTGATTATGGTACCTACAAGAA CACTTGTGATGGTAACACCTTTACATATGCATCTGCACTCTGGGAAATCCAGCAAGTTGTTGATGCGGATA GCAAGATTGTTCAACTTAGTGAAATTAACATGGACAATTCACCAAATTTGGCTTGGCCTCTTATTGTTACA GCTCTAAGAGCCAACTCAGCTGTTAAACTACAGAATAATGAACTGAGTCCAGTAGCACTACGACAGATGTC CTGTGCGGCTGGTACCACACAAACAGCTTGTACTGATGACAATGCACTTGCCTACTATAACAATTCGAAGG GAGGTAGGTTTGTGCTGGCATTACTATCAGACCACCAAGATCTCAAATGGGCTAGATTCCCTAAGAGTGAT AGTGAAATACTTGTACTTCATCAAAGGCTTAAACAACCTAAATAGAGGTATGGTGCTGGGCAGTTTAGCTG  $\tt CTACAGTACGTCTTCAGGCTGGAAATGCTACAGAAGTACCTGCCAATTCAACTGTGCTTTCCTTCTGTGCT-$ TTTGCAGTAGACCCTGCTAAAGCATATAAGGATTACCTAGCAAGTGGAGACAACCAATCACCAACTGTGT GAAGATGTTGTGTACACACTGGTACAGGACAGGCAATTACTGTAACACCAGAAGCTAACATGGACCAAG **AGTCCTTTGGTGGTGCTTCATGTTGTCTGTATTGTAGATGCCACATTGACCATCCAAATCCTAAAGGATTC** TGTGACTTGAAAGGTAAGTACGTCCAAATACCTACCACTTGTGCTAATGACCCAGTGGGTTTTACACTTAG AAACACAGTCTGTACCGTCTGCGGAATGTGGAAAGGTTATGGCTGTAGTTGTGACCAACTCCGCGAACCCT TGATGCAGTCTGCGGATGCATCAACGTTTTTAAACGGGTTTGCGGTGTAAGTGCAGCCCGTCTTACACCGT GCGGCACAGGCACTAGTACTGATGTCGTCTACAGGGCTTTTGATATTTACAACGAAAAAGTTGCTGGTTTT GCAAAGTTCCTAAAAACTAATTGCTGTCGCTTCCAGGAGAAGGATGAGGAAGGCAATTTATTAGACTCTTA CTTTGTAGTTAAGAGGCATACTATGTCTAACTACCAACATGAAGAGACTATTTATAACTTGGTTAAAGATT GTCCAGCGGTTGCTGCCATGACTTTTTCAAGTTTAGAGTAGATGGTGACATGGTACCACATATATCACGT CAGCGTCTAACTAAATACACAATGGCTGATTTAGTCTATGCTCTACGTCATTTTGATGAGGGTAATTGTGA TACATTAAAAGAAATACTCGTCACATACAATTGCTGTGATGATGATTATTTCAATAAGAAGGATTGGTATG ACTTCGTAGAGAATCCTGACATCTTACGCGTATATGCTAACTTAGGTGAGCGTGTACGCCAATCATTATTA AAGACTGTACAATTCTGCGATGCTATGCGTGATGCAGGCATTGTAGGCGTACTGACATTAGATAATCAGGA TCTTAATGGGAACTGGTACGATTTCGGTGATTTCGTACAAGTAGCACCAGGCTGCGGAGTTCCTATTGTGG ATTCATATTACTCATTGCTGATGCCCATCCTCACTTTGACTAGGGCATTGGCTGCTGAGTCCCATATGGAT GCTGATCTCGCAAAACCACTTATTAAGTGGGATTTGCTGAAATATGATTTTACGGAAGAGAGACTTTGTCT GTATCCTTCATTGTGCAAACTTTAATGTGTTATTTTCTACTGTGTTTTCCACCTACAAGTTTTGGACCACTA GTAAGAAAATATTTGTAGATGGTGTTCCTTTTGTTGTTTCAACTGGATACCATTTTCGTGAGTTAGGAGT CGTACATAATCAGGATGTAAACTTACATAGCTCGCGTCTCAGTTTCAAGGAACTTTTAGTGTATGCTGCTG ATCCAGCTATGCATGCAGCTTCTGGCAATTTATTGCTAGATAAACGCACTACATGCTTTTCAGTAGCTGCA CTAACAAACAATGTTGCTTTTCAAACTGTCAAACCCGGTAATTTTAATAAAGACTTTTATGACTTTGCTGT GTCTAAAGGTTTCTTTAAGGAAGGAAGTTCTGTTGAACTAAAACACTTCTTCTTTGCTCAGGATGGCAACG CTGCTATCAGTGATTATGACTATTATCGTTATAATCTGCCAACAATGTGTGATATCAGACAACTCCTATTC TAACAATCTGGATAAATCAGCTGGTTTCCCATTTAATAAATGGGGTAAGGCTAGACTTTATTATGACTCAA TGAGTTATGAGGATCAAGATGCACTTTTCGCGTATACTAAGCGTAATGTCATCCCTACTATAACTCAAATG AATCTTAAGTATGCCATTAGTGCAAAGAATAGAGCTCGCACCGTAGCTGGTGTCTCTATCTGTAGTACTAT GACAAATAGACAGTTTCATCAGAAATTATTGAAGTCAATAGCCGCCACTAGAGGAGCTACTGTGGTAATTG GAACAAGCAAGTTTTACGGTGGCTGGCATAATATGTTAAAAACTGTTTACAGTGATGTAGAAACTCCACAC CTTATGGGTTGGGATTATCCAAAATGTGACAGAGCCATGCCTAACATGCTTAGGATAATGGCCTCTCTTGT TCTTGCTCGCAAACATAACACTTGCTGTAACTTATCACACCGTTTCTACAGGTTAGCTAACGAGTGTGCGC AAGTATTAAGTGAGATGGTCATGTGTGGCGGCTCACTATATGTTAAACCAGGTGGAACATCATCCGGTGAT GCTACAACTGCTTATGCTAATAGTGTCTTTAACATTTGTCAAGCTGTTACAGCCAATGTAAATGCACTTCT TTCAACTGATGGTAATAAGATAGCTGACAAGTATGTCCGCAATCTACAACACAGGCTCTATGAGTGTCTCT ATAGAAATAGGGATGTTGATCATGAATTCGTGGATGAGTTTTACGCTTACCTGCGTAAACATTTCTCCATG TAAGAACTTTAAGGCAGTTCTTTATTATCAAAATAATGTGTTCATGTCTGAGGCAAAATGTTGGACTGAGA CTGACCTTACTAAAGGACCTCACGAATTTTGCTCACAGCATACAATGCTAGTTAAACAAGGAGATGATTAC GTGTACCTGCCTTACCCAGATCCATCAAGAATATTAGGCGCAGGCTGTTTTGTCGATGATATTGTCAAAAAC AGATGGTACACTTATGATTGAAAGGTTCGTGTCACTGGCTATTGATGCTTACCACTTACAAAACATCCTA ATCAGGAGTATGCTGATGTCTTTCACTTGTATTTACAATACATTAGAAAGTTACATGATGAGCTTACTGGC CACATGTTGGACATGTATTCCGTAATGCTAACTAATGATAACACCTCACGGTACTGGGAACCTGAGTTTTA TGAGGCTATGTACACACCACATACAGTCTTGCAGGCTGTAGGTGCTTGTGTATTGTGCAATTCACAGACTT

CACTTCGTTGCGGTGCCTGTATTAGGAGACCATTCCTATGTTGCAAGTGCTGCTATGACCATGTCATTTCA ACATCACACAAATTAGTGTTGTCTGTTAATCCCTATGTTTGCAATGCCCCAGGTTGTGATGTCACTGATGT GACACAACTGTATCTAGGAGGTATGAGCTATTATTGCAAGTCACATAAGCCTCCCATTAGTTTTCCATTAT GTGCTAATGGTCAGGTTTTTGGTTTATACAAAAACACATGTGTAGGCAGTGACAATGTCACTGACTTCAAT GCGAAGTACTCTCTGACAGAGAATTGCATCTTTCATGGGAGGTTGGAAAACCTAGACCACCATTGAACAGA AACTATGTCTTTACTGGTTACCGTGTAACTAAAAATAGTAAAGTACAGATTGGAGAGTACACCTTTGAAAA AGGTGACTATGGTGATGCTGTTGTGTACAGAGGTACTACGACATACAAGTTGAATGTTGGTGATTACTTTG TGTTGACATCTCACACTGTAATGCCACTTAGTGCACCTACTCTAGTGCCACAAGAGCACTATGTGAGAATT ACTGGCTTGTACCCAACACTCAACATCTCAGATGAGTTTTCTAGCAATGTTGCAAATTATCAAAAGGTCGG CATGCAAAAGTACTCTACACTCCAAGGACCACCTGGTACTGGTAAGAGTCATTTTGCCATCGGACTTGCTC TCTATTACCCATCTGCTCGCATAGTGTATACGGCATGCTCTCATGCAGCTGTTGATGCCCCTATGTGAAAAG GCATTAAAATATTTGCCCATAGATAAATGTAGTAGAATCATACCTGCGCGTGCGCGCGTAGAGTGTTTTGA TAAATTCAAAGTGAATTCAACACTAGAACAGTATGTTTTCTGCACTGTAAATGCATTGCCAGAAACAACTG  $\tt CTGACATTGTAGTCTTTGATGAAATCTCTATGGCTACTAATTATGACTTGAGTGTTGTCAATGCTAGACTT$ CGTGCAAAACACTACGTCTATATTGGCGATCCTGCTCAATTACCAGCCCCCGCACATTGCTGACTAAAGG CACACTAGAACCAGAATATTTTAATTCAGTGTGCAGACTTATGAAAACAATAGGTCCAGACATGTTCCTTG GAACTTGTCGCCGTTGTCCTGCTGAAATTGTTGACACTGTGAGTGCTTTAGTTTATGACAATAAGCTAAAA GCACACAAGGATAAGTCAGCTCAATGCTTCAAAATGTTCTACAAAGGTGTTATTACACATGATGTTTCATC TGCAATCAACAGACCTCAAATAGGCGTTGTAAGAGAATTTCTTACACGCAATCCTGCTTGGAGAAAAGCTG TTTTTATCTCACCTTATAATTCACAGAACGCTGTAGCTTCAAAAATCTTAGGATTGCCTACGCAGACTGTT GATTCATCACAGGGTTCTGAATATGACTATGTCATATTCACACAAACTACTGAAACAGCACACTCTTGTAA TGTCAACCGCTTCAATGTGGCTATCACAAGGGCAAAAATTGGCATTTTGTGCATAATGTCTGATAGAGATC TTTATGACAAACTGCAATTTACAAGTCTAGAAATACCACGTCGCAATGTGGCTACATTACAAGCAGAAAAT GTAACTGGACTTTTTAAGGACTGTAGTAAGATCATTACTGGTCTTCATCCTACACAGGCACCTACACACCCT CAGCGTTGATATAAAGTTCAAGACTGAAGGATTATGTGTTGACATACCAGGCATACCAAAGGACATGACCT ACCGTAGACTCATCTCTATGATGGGTTTCAAAATGAATTACCAAGTCAATGGTTACCCTAATATGTTTATC ACCCGCGAAGAAGCTATTCGTCACGTTCGTGCGTGGATTGGCTTTGATGTAGAGGGCTGTCATGCAACTAG AGATGCTGTGGGTACTAACCTACCTCTCCAGCTAGGATTTTCTACAGGTGTTAACTTAGTAGCTGTACCGA CTGGTTATGTTGACACTGAAAATAACACAGAATTCACCAGAGTTAATGCAAAACCTCCACCAGGTGACCAG TTTAAACATCTTATACCACTCATGTATAAAGGCTTGCCCTGGAATGTAGTGCGTATTAAGATAGTACAAAT GCTCAGTGATACACTGAAAGGATTGTCAGACAGAGTCGTGTTCGTCCTTTGGGCGCATGGCTTTGAGCTTA CATCAATGAAGTACTTTGTCAAGATTGGACCTGAAAGAACGTGTTGTCTGTGTGACAAACGTGCAACTTGC TTTTCTACTTCATCAGATACTTATGCCTGGGAATCATTCTGTGGGTTTTGACTATGTCTATAACCCATT TATGATTGATGTTCAGCAGTGGGGCTTTACGGGTAACCTTCAGAGTAACCATGACCAACATTGCCAGGTAC ATGGAAATGCACATGTGGCTAGTTGTGATGCTATCATGACTAGATGTTTAGCAGTCCATGAGTGCTTTGTT AAGCGCGTTGATTGGTCTGTTGAATACCCTATTATAGGAGATGAACTGAGGGTTAATTCTGCTTGCAGAAA AGTACAACACATGGTTGTGAAGTCTGCATTGCTTGCTGATAAGTTTCCAGTTCTTCATGACATTGGAAAATC AAAGCTTACAAAATAGAGGAACTCTTCTATTCTTATGCTACACATCACGATAAATTCACTGATGGTGTTTG TTTGTTTTGGAATTGTAACGTTGATCGTTACCCAGCCAATGCAATTGTGTGTAGGTTTGACACAAGAGTCT GTCTCATGGCAAACAAGTAGTGTCGGATATTGATTATGTTCCACTCAAATCTGCTACGTGTATTACACGAT GCAATTTAGGTGGTGCTGTTTGCAGACACCATGCAAATGAGTACCGACAGTACTTGGATGCATATAATATG ATGATTTCTGCTGGATTTAGCCTATGGATTTACAAACAATTTGATACTTATAACCTGTGGAATACATTTAC CAGGTTACAGAGTTTAGAAAATGTGGCTTATAATGTTGTTAATAAAGGACACTTTGATGGACACGCCGGCG AAGCACCTGTTTCCATCATTAATAATGCTGTTTACACAAAGGTAGATGGTATTGATGTGGAGATCTTTGAA **AATAAGACAACACTTCCTGTTAATGTTGCATTTGAGCTTTGGGCTAAGCGTAACATTAAACCAGTGCCAGA** GATTAAGATACTCAATAATTTGGGTGTTGATATCGCTGCTAATACTGTAATCTGGGACTACAAAAGAGAAG TGTTCTTCACTTACTGTTTGTTTGATGGTAGAGTGGAAGGACAGGTAGACCTTTTTAGAAACGCCCGTAA TGGTGTTTTAATAACAGAAGGTTCAGTCAAAGGTCTAACACCTTCAAAGGGACCAGCACAAGCTAGCGTCA ATGGAGTCACATTAATTGGAGAATCAGTAAAAACACAGTTTAACTACTTTAAGAAAGTAGACGGCATTATT CAACAGTTGCCTGAAACCTACTTTACTCAGAGCAGAGCTTAGAGGATTTTAAGCCCAGATCACAAATGGA **AACTGACTTTCTCGAGCTCGCTATGGATGAATTCATACAGCGATATAAGCTCGAGGGCTATGCCTTCGAAC** 

#### 11/55

ACATCGTTTATGGAGATTTCAGTCATGGACAACTTGGCGGTCTTCATTTAATGATAGGCTTAGCCAAGCGC TCACAAGATTCACCACTTAAATTAGAGGATTTTATCCCTATGGACAGCACAGTGAAAAATTACTTCATAAC TAATAAAGTCACAAGATTTGTCAGTGATTTCAAAAGTGGTCAAGGTTACAATTGACTATGCTGAAATTTCA ACCAGGTGTTGCGATGCCTAACTTGTACAAGATGCAAAGAATGCTTCTTGAAAAGTGTGACCTTCAGAATT ATGGTGAAAATGCTGTTATACCAAAAGGAATAATGATGAATGTCGCAAAGTATACTCAACTGTGTCAATAC TTAAATACACTTACTTTAGCTGTACCCTACAACATGAGAGTTATTCACTTTGGTGCTGGCTCTGATAAAGG AGTTGCACCAGGTACAGCTGTGCTCAGACAATGGTTGCCAACTGGCACACTACTTGTCGATTCAGATCTTA ATGACTTCGTCTCCGACGCATATTCTACTTTAATTGGAGACTGTGCAACAGTACATACGGCTAATAAATGG GACCTTATTATTAGCGATATGTATGACCCTAGGACCAAACATGTGACAAAAGAGAATGACTCTAAAGAAGG GTTTTTCACTTATCTGTGGGTTTATAAAGCAAAAACTAGCCCTGGGTGGTTCTATAGCTGTAAAGATAA CAGAGCATTCTTGGAATGCTGACCTTTACAAGCTTATGGGCCATTTCTCATGGTGGACAGCTTTTGTTACA AATGTAAATGCATCATCATCGGAAGCATTTTTAATTGGGGCTAACTATCTTGGCAAGCCGAAGGAACAAAT TGATGGCTATACCATGCATGCTAACTACATTTTCTGGAGGAACACAAATCCTATCCAGTTGTCTTCCTATT CACTCTTTGACATGAGCAAATTTCCTCTTAAATTAAGAGGAACTGCTGTAATGTCTCTTAAGGAGAATCAA ATCAATGATATGATTTATTCTCTTCTGGAAAAAGGTAGGCTTATCATTAGAGAAAACAACAGAGTTGTGGT GTAGTGACCTTGACCGGTGCACCACTTTTGATGATGTTCAAGCTCCTAATTACACTCAACATACTTCATCT TCCATTTATTCTAATGTTACAGGGTTTCATACTATTAATCATACGTTTGGCAACCCTGTCATACCTTTTA AGGATGGTATTTATTTTGCTGCCACAGAGAAATCAAATGTTGTCCGTGGTTGGGTTTTTGGTTCTACCATG AACAACAGTCACAGTCGGTGATTATTATTAACAATTCTACTAATGTTGTTATACGAGCATGTAACTTTGA ATTGTGTGACAACCCTTTCTTTGCTGTTTCTAAACCCATGGGTACACAGACACATACTATGATATTCGATA ATGCATTTAATTGCACTTTCGAGTACATATCTGATGCCTTTTCGCTTGATGTTTCAGAAAAGTCAGGTAAT TTTAAACACTTACGAGAGTTTGTGTTTAAAAATAAAGATGGGTTTCTCTATGTTTATAAGGGCTATCAACC TATAGATGTAGTTCGTGATCTACCTTCTGGTTTTAACACTTTGAAACCTATTTTTAAGTTGCCTCTTGGTA TTAACATTACAAATTTTAGAGCCATTCTTACAGCCTTTTCACCTGCTCAAGACATTTGGGGCACGTCAGCT GCAGCCTATTTTGTTGGCTATTTAAAGCCAACTACATTTATGCTCAAGTATGATGAAAATGGTACAATCAC AGATGCTGTTGATTGTTCTCAAAATCCACTTGCTGAACTCAAATGCTCTGTTAAGAGCTTTTGAGATTGACA AAGGAATTTACCAGACCTCTAATTTCAGGGTTGTTCCCTCAGGAGATGTTGTGAGATTCCCTAATATTACA AACTTGTGTCTTTTGGAGAGGTTTTTAATGCTACTAAATTCCCTTCTGTCTATGCATGGGAGAGAAAAAA AATTTCTAATTGTGTTGCTGATTACTCTGTGCTCTACAACATCAACATTTTTTTCAACCTTTAAGTGCTATG GCGTTTCTGCCACTAAGTTGAATGATCTTTGCTTCTCCAATGTCTATGCAGATTCTTTTGTAGTCAAGGGA GATGATGTAAGACAAATAGCGCCAGGACAAACTGGTGTTATTGCTGATTATAAATTAAATTGCCAGATGA TTTCATGGGTTGTGTCCTTGCATAGAATACTAGGAACATTGATGCTACTTCAACTGGTAATTATAATTATA GATGGCAAACCTTGCACCCCACCTGCTCTTAATTGTTATTGGCCATTAAATGATTATGGTTTTTACACCAC ·TTTGTGGACCAAAATTATCCACTGACCTTATTAAGAACCAGTGTGTCAATTTTAATTTAATTGGACTCACT GGTACTGGTGTGTTAACTCCTTCTTCAAAGAGATTTCAACCATTTCAACAATTTGGCCGTGATGTTTCTGA TTTCACTGATTCCGTTCGAGATCCTAAAACATCTGAAATATTAGACATTTCACCTTGCGCTTTTGGGGGGTG TAAGTGTAATTACACCTGGAACAAATGCTTCATCTGAAGTTGCTGTTCTATATCAAGATGTTAACTGCACT GATGTTTCTACAGCAATTCATGCAGATCAACTCACACCAGCTTGGCGCATATATTCTACTGGAAACAATGT ATTCCAGACTCAAGCAGGCTGTCTTATAGGAGCTGAGCATGTCGACACTTCTTATGAGTGCGACATTCCTA TTGGAGCTGGCATTTGTGCTAGTTACCATACAGTTTCTTTATTACGTAGTACTAGCCAAAAATCTATTGTG GCTTATACTATGTCTTTAGGTGCTGATAGTTCAATTGCTTACTCTAATAACACCATTGCTATACCTACTAA CTTTTCAATTAGCATTACTACAGAAGTAATGCCTGTTTCTATGGCTAAAACCTCCGTAGATTGTAATATGT ACATCTGCGGAGATTCTACTGAATGTGCTAATTTGCTTCTCCAATATGGTAGCTTTTGCACACAACTAAAT GTACAAAACCCCAACTTTGAAATATTTTGGTGGTTTTAATTTTTCACAAATATTACCTGACCCTCTAAAGC CAACTAAGAGGTCTTTTATTGAGGACTTGCTCTTTAATAAGGTGACACTCGCTGATGCTGGCTTCATGAAG CANTATGGCGAATGCCTAGGTGATATTAATGCTAGAGATCTCATTTGTGCGCAGAAGTTCAATGGACTTAC  $\tt CTGCTGGATGGACATTTGGTGCTGGCGCTGCTCTTCAAATACCTTTTGCTATGCAAATGGCATATAGGTTC$ GATTAGTCAAATTCAAGAATCACTTACAACAACATCAACTGCATTGGGCAAGCTGCAAGACGTTGTTAACC

AGAATGCTCAAGCATTAAACACTTGTTAAACAACTTAGCTCTAATTTTGGTGCAATTTCAAGTGTGCTA AATGATATCCTTTCGCGACTTGATAAAGTCGAGGCGGAGGTACAAATTGACAGGTTAATTACAGGCAGACT TCAAAGCCTTCAAACCTATGTAACACAACAACTAATCAGGGCTGCTGAAATCAGGGCTTCTGCTAATCTTG CTGCTACTAAAATGTCTGAGTGTTCTTGGACAATCAAAAAGAGTTGACTTTTGTGGAAAGGGCTACCAC CTTATGTCCTTCCCACAGCAGCCCCGCATGGTGTTGTCTTCCTACATGTCACGTATGTGCCATCCCAGGA GAGGAACTTCACCACAGCGCCAGCAATTTGTCATGAAGGCAAAGCATACTTCCCTCGTGAAGGTGTTTTTG TGTTTAATGGCACTTCTTGGTTTATTACACAGAGGAACTTCTTTTCTCCACAAATAATTACTACAGACAAT ACATTTGTCTCAGGAAATTGTGATGTCGTTATTGGCATCATTAACAACACAGTTTATGATCCTCTGCAACC TGAGCTTGACTCATTCAAAGAAGAGCTGGACAAGTACTTCAAAAATCATACATCACCAGATGTTGATCTTG GCGACATTTCAGGCATTAACGCTTCTGTCGTCAACATTCAAAAAGAAATTGACCGCCTCAATGAGGTCGCT GTATGTTTGGCTCGGCTTCATTGCTGGACTAATTGCCATCGTCATGGTTACAATCTTGCTTTGTTGCATGA CTAGTTGTTGCAGTTGCCTCAAGGGTGCATGCTCTTGTGGTTCTTGCTGCAAGTTTGATGAGGATGACTCT GAGCCAGTTCTCAAGGGTGTCAAATTACATTACACATAAACGAACTTATGGATTTGTTTATGAGATTTTTT ACTCTTGGATCAATTACTGCACAGCCAGTAAAAATTGACAATGCTTCTCCTGCAAGTACTGTTCATGCTAC AGCAACGATACCGCTACAAGCCTCACTCCCTTTCGGATGGCTTGTTATTGGCGTTTGCATTTCTTGCTGTTT TTCAGAGCGCTACCAAAATAATTGCGCTCAATAAAAGATGGCAGCTAGCCCTTTATAAGGGCTTCCAGTTC ATTTGCAATTTACTGCTGCTATTTGTTACCATCTATTCACATCTTTTGCTTGTCGCTGCAGGTATGGAGGC GCAATTTTTGTACCTCTATGCCTTGATATATTTTTCTACAATGCATCAACGCATGTAGAATTATTATGAGAT ACACATAACTATGACTACTGTATACCATATAACAGTGTCACAGATACAATTGTCGTTACTGAAGGTGACGG CATTTCAACACCAAAACTCAAAGAAGACTACCAAATTGGTGGTTATTCTGAGGATAGGCACTCAGGTGTTA AAGACTATGTCGTTGTACATGGCTATTTCACCGAAGTTTACTACCAGCTTGAGTCTACACAAATTACTACA GACACTGGTATTGAAAATGCTACATTCTTCATCTTTAACAAGCTTGTTAAAGACCCACCGAATGTGCAAAT ACACAATCGACGGCTCTTCAGGAGTTGCTAATCCAGCAATGGATCCAATTTATGATGAGCCGACGACGA CTACTAGCGTGCCTTTGTAAGCACAAGAAAGTGAGTACGAACTTATGTACTCATTCGTTTCGGAAGAAACA GGTACGTTAATAGTTAATAGCGTACTTCTTTTTTTTTTCTTGCTGGTATTCTTGCTAGTCACACTAGCCAT  ${\tt CCTTACTGCGCTTCGATTGTGTGCGTACTGCTGCAATATTGTTAACGTGAGTTTAGTAAAACCAACGGTTT}$ ACGTCTACTCGCGTGTTAAAAATCTGAACTCTTCTGAAGGAGTTCCTGATCTTCTGGTCTAAACGAACTAA CTATTATTATTATTCTGTTTGGAACTTTAACATTGCTTATCATGGCAGACAACGGTACTATTACCGTTGAG GAGCTTAAACAACTCCTGGAACAATGGAACCTAGTAATAGGTTTCCTAGTCTAGCCTGGATTATGTTACT ACAATTTGCCTATTCTAATCGGAACAGGTTTTTGTACATAATAAAGCTTGTTTTCCTCTGGCTCTTGTGGC CCGCTCAATGTGGTCATTCAACCCAGAAACAAACATTCTTCTCAATGTGCCTCTCCGGGGGACAATTGTGA CCAGACCGCTCATGGAAAGTGAACTTGTCATTGGTGCTGTGATCATTCGTGGTCACTTGCGAATGGCCGGA CACTCCCTAGGGCGCTGTGACATTAAGGACCTGCCAAAAGAGATCACTGTGGCTACATCACGAACGCTTTC TTATTACAAATTAGGAGCGTCGCAGCGTGTAGGCACTGATTCAGGTTTTGCTGCATACAACCGCTACCGTA TTGGAAACTATAAATTAAATACAGACCACGCCGGTAGCAACGACAATATTGCTTTGCTAGTACAGTAAGTG ACAACAGATGTTTCATCTTGTTGACTTCCAGGTTACAATAGCAGAGATATTGATTATCATTATGAGGACTT TCAGGATTGCTATTTGGAATCTTGACGTTATAATAAGTTCAATAGTGAGACAATTATTTAAGCCTCTAACT AAGAAGAATTATTCGGAGTTAGATGATGAAGAACCTATGGAGTTAGATTATCCATAAAACGAACATGAAAA TTATTCTCTTCCTGACATTGATTGTATTTACATCTTGCGAGCTATATCACTATCAGGAGTGTGTTAGAGGT ACGACTGTACTACTAAAAGAACCTTGCCCATCAGGAACATACGAGGGCAATTCACCATTTCACCCTCTTGC TGACAATAAATTTGCACTAACTTGCACTAGCACACTTTGCTTTTGCTTGTGCTGACGGTACTCGACATA CCTATCAGCTGCGTGCAAGATCAGTTTCACCAAAACTTTTCATCAGACAAGAGGAGGTTCAACAAGAGCTC TACTCGCCACTTTTTCTCATTGTTGCTGCTCTAGTATTTTTAATACTTTGCTTCACCATTAAGAGAAAAGAC AGAATGAATGAGCTCACTTTAATTGACTTCTATTTGTGCTTTTTAGCCTTTCTGCTATTCCTTGTTTTAAT AATGCTTATTATATTTTGGTTTTCACTCGAAATCCAGGATCTAGAAGAACCTTGTACCAAAGTCTAAACGA ACATGAAACTTCTCATTGTTTTGACTTGTATTTCTCTATGCAGTTGCATATGCACTGTAGTACAGCGCTGT GCATCTAATAAACCTCATGTGCTTGAAGATCCTTGTAAGGTACAACACTAGGGGTAATACTTATAGCACTG CTTGGCTTTGTGCTCTAGGAAAGGTTTTACCTTTTCATAGATGGCACACTATGGTTCAAACATGCACACCT AATGTTACTATCAACTGTCAAGATCCAGCTGGTGGTGCGCTTATAGCTAGGTGTTGGTACCTTCATGAAGG GGACCCCAATCAAACCAACGTAGTGCCCCCCGCATTACATTTGGTGGACCCACAGATTCAACTGACAATAA CCAGAATGGAGGACGCAATGGGGCAAGGCCAAAACAGCGCCGACCCCAAGGTTTACCCAATAATACTGCGT CTTGGTTCACAGCTCTCACTCAGCATGGCAAGGAGGAACTTAGATTCCCTCGAGGCCAGGGCGTTCCAATC

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AACACCAATAGTGGTCCAGATGACCAAATTGGCTACTACCGAAGAGCTACCCGACGAGTTCGTGGTGGTGA CGGCAAAATGAAAGAGCTCAGCCCCAGATGGTACTTCTATTACCTAGGAACTGGCCCAGAAGCTTCACTTC CCTACGGCGCTAACAAGAAGGCATCGTATGGGTTGCAACTGAGGGAGCCTTGAATACACCCAAAGACCAC ATTGGCACCGCAATCCTAATAACAATGCTGCCACCGTGCTACAACTTCCTCAAGGAACAACATTGCCAAA AGGCTTCTACGCAGAGGGAAGCAGAGGCGGCAGTCAAGCCTCTTCTCGCTCCTCATCACGTAGTCGCGGTA ATTCAAGAAATTCAACTCCTGGCAGCAGTAGGGGAAATTCTCCTGCTCGAATGGCTAGCGGAGGTGGTGAA ACTGCCCTCGCGCTATTGCTGCTAGACAGATTGAACCAGCTTGAGAGCAAAGTTTCTGGTAAAGGCCAACA ACAACAAGGCCAAACTGTCACTAAGAAATCTGCTGCTGAGGCATCTAAAAAGCCTCGCCAAAAACGTACTG CCACAAAACAGTACAACGTCACTCAAGCATTTGGGAGACGTGGTCCAGAACAAACCCAAGGAAATTTCGGG GACCAAGACCTAATCAGACAAGGAACTGATTACAAACATTGGCCGCAAATTGCACAATTTGCTCCAAGTGC CTCTGCATTCTTTGGAATGTCACGCATTGGCATGGAAGTCACACCTTCGGGAACATGGCTGACTTATCATG GAGCCATTAAATTGGATGACAAAGATCCACAATTCAAAGACAACGTCATACTGCTGAACAAGCACATTGAC · GCATACAAAACATTCCCACCAACAGAGCCTAAAAAGGACAAAAAGAAAAAGACTGATGAAGCTCAGCCTTT GCCGCAGAGACAAAAGAAGCAGCCCACTGTGACTCTTCTTCCTGCGGCTGACATGGATGATTTCTCCAGAC TCTCGTAACTAAACAGCACAAGTAGGTTTAGTTAACTTTAATCTCACATAGCAATCTTTAATCAATGTGTA ACATTAGGGAGGACTTGAAAGAGCCACCACATTTTCATCGAGGCCACGCGGAGTACGATCGAGGGTACAGT 

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CTACCCAGGAAAAGCCAACCACCTCGATCTCTTGTAGATCTGTTCTCTAAAACGAACTTTAAAATCTGTGT AGCTGTCGCTCGCTGCATGCCTAGTGCACCTACGCAGTATAAACAATAATAAATTTTACTGTCGTTGACA AGAAACGAGTAACTCGTCCCTCTTCTGCAGACTGCTTACGGTTTCGTCCGTGTTGCAGTCGATCATCAGCA TACCTAGGTTTCGTCCGGGTGTGACCGAAAGGTAAGATGGAGAGCCTTGTTCTTGGTGTCAACGAGAAAAC ACACGTCCAACTCAGTTTGCCTGTCCTTCAGGTTAGAGACGTGCTAGTGCGTGGCTTCGGGGACTCTGTGG AAGAGGCCCTATCGGAGGCACGTGAACACCTCAAAAATGGCACTTGTGGTCTAGTAGAGCTGGAAAAAAGGC GTACTGCCCCAGCTTGAACAGCCCTATGTGTTCATTAAACGTTCTGATGCCTTAAGCACCAATCACGGCCA CAAGGTCGTTGAGCTGGTTGCAGAAATGGACGGCATTCAGTACGGTCGTAGCGGTATAACACTGGGAGTAC TCGTGCCACATGTGGGCGAAACCCCAATTGCATACCGCAATGTTCTTCTTCGTAAGA'ACGGTAATAAGGGA GCCGGTGGTCATAGCTATGGCATCGATCTAAAGTCTTATGACTTAGGTGACGAGCTTGGCACTGATCCCAT ATGGAGGTGCAGTCACTCGCTATGTCGACAACAATTTCTGTGGCCCAGATGGGTACCCTCTTGATTGCATC AAAGATTTTCTCGCACGCGGGCAAGTCAATGTGCACTCTTTCCGAACAACTTGATTACATCGAGTCGAA GAGAGGTGTCTACTGCTGCCGTGACCATGAGCATGAAATTGCCTGGTTCACTGAGCGCTCTGATAAGAGCT ACGAGCACCAGACACCCTTCGAAATTAAGAGTGCCAAGAAATTTGACACTTTCAAAGGGGAATGCCCAAAG TTTGTGTTTCCTCTTAACTCAAAAGTCAAAGTCATTCAACCACGTGTTGAAAAAGAAAAAAGACTGAG**GGTTT** CATGGGGCGTATACGCTCTGTGTACCCTGTTGCATCTCCACAGGAGTGTAACAATATGCACTTGT**CTACCT** TGATGAAATGTAATCATTGCGATGAAGTTTCATGGCAGACGTGCGACTTTCTGAAAGCCACTTGT<mark>GAACAT</mark> AATGCCATGTCCTGCCTGTCAAGACCCAGAGATTGGACCTGAGCATAGTGTTGCAGATTATCACAACCACT CAAACATTGAAACTCGACTCCGCAAGGGAGGTAGGACTAGATGTTTTTGGAGGCTGTGTGTTT**TGCCTATGTT** GGCTGCTATAATAAGCGTGCCTACTGGGTTCCTCGTGCTAGTGCTGATATTGGCTCAGGCCATACTGGCAT TACTGGTGACAATGTGGAGACCTTGAATGAGGATCTCCTTGAGATACTGAGTCGTGAACGTGTTAACATTA ACATTGTTGGCGATTTTCATTTGAATGAAGAGGTTGCCATCATTTTGGCATCTTTCTCTGCTTCTACAAGT GCCTTTATTGACACTATAAAGAGTCTTGATTACAAGTCTTTCAAAACCATTGTTGAGTCCTGCGGTAACTA TAAAGTTACCAAGGGAAAGCCCGTAAAAGGTGCTTGGAACATTGGACAACAGAGATCAGTTTTAACACCAC TGTGTGGTTTTCCCTCACAGGCTGCTGGTGTTATCAGATCAATTTTTGCGCGCACACTTGATGCAGCAAAC CACTCAATTCCTGATTTGCAAAGAGCAGCTGTCACCATACTTGATGGTATTTCTGAACAGTCATTACGTCT TGTCGACGCCATGGTTTATACTTCAGACCTGCTCACCAACAGTGTCATTATTATGGCATATGTAACTGGTG GTCTTGTACAACAGACTTCTCAGTGGTTGTCTAATCTTTTGGGCACTACTGTTGAAAAACTCAGGCCTATC TTTGAATGGATTGAGGCGAAACTTAGTGCAGGAGTTGAATTTCTCAAGGATGCTTGGGAGATTCT**CAAATT** TCTCATTACAGGTGTTTTTGACATCGTCAAGGGTCAAATACAGGTTGCTTCAGATAACATCAAGGATTGTG TAAAATGCTTCATTGATGTTGTTAACAAGGCACTCGAAATGTGCATTGATCAAGTCACTATCGCTGGCGCA AAGTTGCGATCACTCAACTTAGGTGAAGTCTTCATCGCTCAAAGCAAGGGACTTTACCGTCAGTGTATACG TGGCAAGGAGCAGCTGCAACTACTCATGCCTCTTAAGGCACCAAAAGAAGTAACCTTTCTTGAAGGTGATT CACATGACACAGTACTTACCTCTGAGGAGGTTGTTCTCAAGAACGGTGAACTCGAAGCACTCGAGACGCCC GTTGATAGCTTCACAAATGGAGCTATCGTTGGCACACCAGTCTGTGTAAATGGCCTCATGCTCTTAGAGAT GGGGTGCACCAATTAAAGGTGTAACCTTTGGAGAAGATACTGTTTGGGAAGTTCAAGGTTACAAGAATGTG AGAATCACATTTGAGCTTGATGAACGTGTTGACAAAGTGCTTAATGAAAAGTGCTCTGTCTACACTGT**TGA** ATCCGGTACCGAAGTTACTGAGTTTGCATGTGTTGTAGCAGAGGCTGTTGTGAAGACTTTACAACCAGTTT CTGATCTCCTTACCAACATGGGTATTGATCTTGATGAGTGGAGTGTAGCTACATTCTACTTATTTGATGAT GCTGGTGAAGAAACTTTTCATCACGTATGTATTGTTCCTTTTACCCTCCAGATGAGGAAGAAGAAGACGACGA TGCAGAGTGTGAGGAAGAAGAAATTGATGAAACCTGTGAACATGAGTACGGTACAGAGGATGATTA**TCAAG** GTCTCCCTCTGGAATTTGGTGCCTCAGCTGAAACAGTTCGAGTTGAGGAAGAAGAAGAGAGAAGACTGGCTG GATGATACTACTGAGCAATCAGAGATTGAGCCAGAACCAGAACCTACACCTGAAGAACCAGTTAATCAGTT TACTGGTTATTTAAAACTTACTGACAATGTTGCCATTAAATGTGTTGACATCGTTAAGGAGGCACAAAGTG CTAATCCTATGGTGATTGTAAATGCTGCTAACATACACCTGAAACATGGTGGTGGTGTAGCAGGTGCACTC AACAAGGCAACCAATGGTGCCATGCAAAAGGAGAGTGATGATTACATTAAGCTAAATGGCCCTCTTACAGT AGGAGGGTCTTGTTTGCTTTCTGGACATAATCTTGCTAAGAAGTGTCTGCATGTTGTTGGACCTAACCTAA ATGCAGGTGAGGACATCCAGCTTCTTAAGGCAGCATATGAAAATTTCAATTCACAGGACATCTTACTTGCA TACACAGGTTTATATTGCAGTCAATGACAAAGCTCTTTATGAGCAGGTTGTCATGGATTATCTTGATAACC TGAAGCCTAGAGTGGAAGCACCTAAACAAGAGGAGCCACCAAACACAGAAGATTCCAAAACTGAGGAGAAA TCTGTCGTACAGAAGCCTGTCGATGTGAAGCCAAAAATTAAGGCCTGCATTGATGAGGTTACCACAACACT GGAAGAAACTAAGTTTCTTACCAATAAGTTACTCTTGTTTGCTGATATCAATGGTAAGCTTTACCATGATT CTCAGAACATGCTTAGAGGTGAAGATATGTCTTTCCTTGAGAAGGATGCACCTTACATGGTAGGTGATGTT ATCACTAGTGGTGATATCACTTGTGTTGTAATACCCTCCAAAAAGGCTGGTGGCACTACTGAGATGCTCTC AAGAGCTTTGAAGAAAGTGCCAGTTGATGAGTATATAACCACGTACCCTGGACAAGGATGTGCTGGTTATA CACTTGAGGAAGCTAAGACTGCTCTTAAGAAATGCAAATCTGCATTTTATGTACCTTCAGAAGCACCT AAGAAAATTAATGCCTATATGCATGGATGTTAGAGCCATAATGGCAACCATCCAACGTAAGTATAAAGGAA TTAAAATTCAAGAGGGCATCGTTGACTATGGTGTCCGATTCTTCTTTTATACTAGTAAAGAGCCTGTAGCT TCTATTATTACGAAGCTGAACTCTCTAAATGAGCCGCTTGTCACAATGCCAATTGGTTATGTGACACATGG ACAGTTTCTTTGGCTGGCTCTTACAGAGATTGGTCCTATTCAGGACAGCGTACAGAGTTAGGTGTTGAATT TCTTAAGCGTGGTGACAAAATTGTGTACCACACTCTGGAGAGCCCCGTCGAGTTTCATCTTGACGGTGAGG TTCTTTCACTTGACAAACTAAAGAGTCTCTTATCCCTGCGGGAGGTTAAGACTATAAAAGTGTTCACAACT GTGGACAACACTAATCTCCACACACACGCTTGTGGATATGTCTATGACATATGGACAGCAGCTTTGGTCCAAC TACCTAGTGATGACACACTACGTAGTGAAGCTTTCGAGTACTACCATACTCTTGATGAGAGTTTTCTTGGT AGGTACATGTCTGCTTTAAACCACACAAAGAAATGGAAATTTCCTCAAGTTGGTGGTTTAACTTCAATTAA ATGGGCTGATAACAATTGTTATTTGTCTAGTGTTTTATTAGCACTTCAACAGCTTGAAGTCAAATTCAATG CACCAGCACTTCAAGAGGCTTATTATAGAGCCCGTGCTGGTGATGCTGCTAACTTTTGTGCACTCATACTC GCTTACAGTAATAAAACTGTTGGCGAGCTTGGTGATGTCAGAGAAACTATGACCCATCTTCTACAGCATGC TAATTTGGAATCTGCAAAGCGAGTTCTTAATGTGGTGTTGTAAACATTGTGGTCAGAAAACTACTACCTTAA CGGGTGTAGAAGCTGTGATGTATATGGGTACTCTATCTTATGATAATCTTAAGACAGGTGTTTCCATTCCA TGTGTGTGTGGTCGTGÅTGCTACACAATATCTAGTACAACAAGAGTCTTCTTTTGTTATGATGTCTGCACC ACCTGCTGAGTATAAATTACAGCAAGGTACATTCTTATGTGCGAATGAGTACACTGGTAACTATCAGTGTG GTCATTACACTCATATAACTGCTAAGGAGACCCTCTATCGTATTGACGGAGCTCACCTTACAAAGATGTCA GAGTACAAAGGACCAGTGACTGATGTTTTCTACAAGGAAACATCTTACACTACAACCATCAAGCCTGTGTC GTATAAACTCGATGGAGTTACTTACACAGAGATTGAACCAAAATTGGATGGGTATTATAAAAAAGGATAATG CTTACTATACAGAGCAGCCTATAGACCTTGTACCAACTCAACCATTACCAAATGCGAGTTTTGATAATTTC AAACTCACATGTTCTAACACAAAATTTGCTGATGATTTAAATCAAATGACAGGCTTCACAAAGCCAGCTTC ACGAGAGCTATCTGTCACATTCTTCCCAGACTTGAATGGCGATGTAGTGGCTATTGACTATAGACACTATT CAGCGAGTTTCAAGAAAGGTGCTAAATTACTGCATAAGCCAATTGTTTGGCACATTAACCAGGCTACAACC AAGACAACGTTCAAACCAAACACTTGGTGTTTACGTTGTCTTTGGAGTACAAAGCCAGTAGATACTTCAAA GTTGTAGGCAATGTCATACTTAAACCATCAGATGAAGGTGTTAAAGTAACACAAGAGTTAGGTCATGAGGA TCTTATGGCTGCTTATGTGGAAAACACAAGCATTACCATTAAGAAACCTAATGAGCTTTCACTAGCCTTAG GTTTAAAAACAATTGCCACTCATGGTATTGCTGCAATTAATAGTGTTCCTTGGAGTAAAATTTTGGCTTAT GTCAAACCATTCTTAGGACAAGCAGCAATTACAACATCAAATTGCGCTAAGAGATTAGCACAACGTGTGTT TAACAATTATATGCCTTATGTGTTTACATTATTGTTCCAATTGTGTACTTTTACTAAAAGTACCAATTCTA GAATTAGAGCTTCACTACCTACAACTATTGCTAAAAATAGTGTTAAGAGTGTTGCTAAAATTATGTTTGGAT GCCGGCATTAATTATGTGAAGTCACCCAAATTTTCTAAATTGTTCACAATCGCTATGTGGCTATTGTTGTT AAGTATTTGCTTAGGTTCTCTAATCTGTGTAACTGCTGCTTTTTGGTGTACTCTTATCTAATTTTGGTGCTC CTTCTTATTGTAATGGCGTTAGAGAATTGTATCTTAATTCGTCTAACGTTACTACTATGGATTTCTGTGAA GGTTCTTTTCCTTGCAGCATTTGTTTAAGTGGATTAGACTCCCTTGATTCTTATCCAGCTCTTGAAACCAT TCAGGTGACGATTTCATCGTACAAGCTAGACTTGACAATTTTAGGTCTGGCCGCTGAGTGGGTTTTTGGCAT ATATGTTGTTCACAAAATTCTTTTATTTATTTAGGTCTTTCAGCTATAATGCAGGTGTTCTTTGGCTATTTT GCTAGTCATTTCATCAGCAATTCTTGGCTCATGTGGTTTATCATTAGTATTGTACAAATGGCACCCGTTTC TGCAATGGTTAGGATGTACATCTTCTTTGCTTCTTTCTACTACATATGGAAGAGCTATGTTCATATCATGG ATGGTTGCACCTCTTCGACTTGCATGATGTGCTATAAGCGCAATCGTGCCACACGCGTTGAGTGTACAACT ATTGTTAATGGCATGAAGAGATCTTTCTATGTCTATGCAAATGGAGGCCGTGGCTTCTGCAAGACTCACAA TGTCACTCCAGTTTAAAAGACCAATCAACCCTACTGACCAGTCATCGTATATTGTTGATAGTGTTGCTGTG AAAAATGGCGCGCTTCACCTCTACTTTGACAAGGCTGGTCAAAAGACCTATGAGAGACATCCGCTCTCCCA TTTTGTCAATTTAGACAATTTGAGAGCTAACAACACTAAAGGTTCACTGCCTATTAATGTCATAGTTTTTG ATGGCAAGTCCAAATGCGACGAGTCTGCTTCTAAGTCTGCTTCTGTGTACTACAGTCAGCTGATGTGCCAA CCTATTCTGTTGCTTGACCAAGCTCTTGTATCAGACGTTGGAGATAGTACTGAAGTTTCCGTTAAGATGTT TGATGCTTATGTCGACACCTTTTCAGCAACTTTTAGTGTTCCTATGGAAAAACTTAAGGCACCTTGTTGCTA CAGCTCACAGCGAGTTAGCAAAGGGTGTAGCTTTAGATGGTGTCCTTTCTACATTCGTGTCAGCTGCCCGA

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CAAGGTGTTGTTGATACCGATGTTGACACAAAGGATGTTATTGAATGTCTCAAACTTTCACATCACTCTGA CTTAGAAGTGACAGGTGACAGTTGTAACAATTTCATGCTCACCTATAATAAGGTTGAAAACATGACGCCCA GAGATCTTGGCGCATGTATTGACTGTAATGCAAGGCATATCAATGCCCAAGTAGCAAAAAGTCACAATGTT TCACTCATCTGGAATGTAAAAGACTACATGTCTTTATCTGAACAGCTGCGTAAACAAATTCGTAGTGCTGC CAAGAAGAACATACCTTTTAGACTAACTTGTGCTACAACTAGACAGGTTGTCAATGTCATAACTACTA AAATCTCACTCAAGGGTGGTAAGATTGTTAGTACTTGTTTTAAACTTATGCTTAAGGCCACATTATTGTGC TGAAATCATTGGTTACAAAGCCATTCAGGATGGTGTCACTCGTGACATCATTTCTAQTGATGATTGTTTTG CAAATAAACATGCTGGTTTTGACGCATGGTTTAGCCAGCGTGGTTGATTCATACAAAAAATGACAAAAGCTGC CCTGTAGTAGCTGCTATCATTACAAGAGAGATTGGTTTCATAGTGCCTGGCTTACCGGGTACTGTGCTGAG AGCAATCAATGGTGACTTCTTGCATTTTCTACCTCGTGTTTTTAGTGCTGTTGGCAACATTTGCTACACAC CTTCCAAACTCATTGAGTATAGTGATTTTGCTACCTCTGCTTGCGTTCTTGCTGCTGAGTGTACAATTTTT AAGGATGCTATGGGCAAACCTGTGCCATATTGTTATGACACTAATTTGCTAGAGGGTTCTATTTCTTATAG TGAGCTTCGTCCAGACACTCGTTATGTGCTTATGGATGGTTCCATCATACAGTTTCCTAACACTTACCTGG AGGGTTCTGTTAGAGTAGTAACAACTTTTGATGCTGAGTACTGTAGACATGGTACATGCGAAAGGTCAGAA GTAGGTATTTGCCTATCTACCAGTGGTAGATGGGTTCTTAATAATGAGCATTACAGAGCTCTATCAGGAGT TTTCTGTGGTGTTGATGCGATGAATCTCATAGCTAACATCTTTACTCCTCTTGTGCAACCTGTGGGTGCTT TAGATGTGTCTGCTTCAGTAGTGGCTGGTGGTATTATTGCCATATTGGTGACTTGTGCTGCCTACTACTTT  ${\tt ATGAAATTCAGACGTGTTTTTGGTGAGTACAACCATGTTGTTGCTGCTAATGCACTTTTGTTTTTGATGTC}$ TTTCACTATACTCTGTCTGGTACCAGCTTACAGCTTTCTGCCGGGAGTCTACTCAGTCTTTTACTTGTACT TGACATTCTATTTCACCAATGATGTTTCATTCTTGGCTCACCTTCAATGGTTTGCCATGTTTTCTCCTATT GTGCCTTTTTGGATAACAGCAATCTATGTATTCTGTATTTCTCTGAAGCACTGCCATTGGTTCTTTAACAA CTATCTTAGGAAAAGAGTCATGTTTAATGGAGTTACATTTAGTACCTTCGAGGAGGCTGCTTTGTGTACCT TTTTGCTCAACAAGGAAATGTACCTAAAATTGCGTAGCGAGACACTGTTGCCACTTACACAGTATAACAGG TATCTTGCTCTATATAACAAGTACAAGTATTTCAGTGGAGCCTTAGATACTACCAGCTATCGTGAAGCAGC AGACATCAATCACTTCTGCTGTTCTGCAGAGTGGTTTTTAGGAAAATGGCATTCCCGTCAGGCAAAGTTGAA GGGTGCATGGTACAAGTAACCTGTGGAACTACAACTCTTAATGGATTGTGGTTGGATGACACAGTATACTG TCCAAGACATGTCATTTGCACAGCAGAAGACATGCTTAATCCTAACTATGAAGATCTGCTCATTCGCAAAT  ${\tt CCAACCATAGCTTCTTGTTCAGGCTGGCAATGTTCAACTTCGTGTTATTGGCCATTCTATGCAAAATTGT}$ CTGCTTAGGCTTAAAGTTGATACTTCTAACCCTAAGACACCCAAGTATAAATTTGTCCGTATCCAACCTGG TCAAACATTTTCAGTTCTAGCATGCTACAATGGTTCACCATCTGGTGTTTATCAGTGTGCCATGAGACCTA ATCATACCATTAAAGGTTCTTTCCTTAATGGATCATGTGGTAGTGTTGGTTTTAACATTGATTATGATTGC GTGTCTTTCTGCTATATGCATCATATGGAGCTTCCAACAGGAGTACACGCTGGTACTGACTTAGAAGGTAA ATTCTATGGTCCATTGTTGACAGACAAACTGCACAGGCTGCAGGTACAGACACAACCATAACATTAAATG TTTTGGCATGGCTGTATGCTGTTATCAATGGTGATAGGTGGTTTCTTAATAGATTCACCACTACTTTG AATGACTTTAACCTTGTGGCAATGAAGTACAACTATGAACCTTTGACACAAGATCATGTTGACATATTGGG ACCTCTTTCTGCTCAAACAGGAATTGCEGTCTTAGATATGTGTGCTGCTTTGAAAGAGCTGCTGCAGAATG GTATGAATGGTCGTACTATCCTTGGTAGCACTATTTTAGAAGATGAGTTTACACCATTTGATGTTAGA CAATGCTCTGGTGTTACCTTCCAAGGTAAGTTCAAGAAAATTGTTAAGGGCACTCATCATTGGATGCTTTT AACTTTCTTGACATCACTATTGATTCTTGTTCAAAGTACACAGTGGTCACTGTTTTTCTTTGTTTACGAGA ATGCTTTCTTGCCATTTACTCTTGGTATTATGGCAATTGCTGCATGTGCTATGCTGCTTGTTAAGCATAAG CACGCATTCTTGTGCTTGTTTCTGTTACCTTCTCTTGCAACAGTTGCTTACTTTAATATGGTCTACATGCC TGCTAGCTGGGTGATGCGTATCATGACATGGCTTGAATTGGCTGACACTAGCTTGTCTGGTTATAGGCTTA AGGATTGTGTTATGTATGCTTCAGCTTTAGTTTTGCTTATTCTCATGACAGCTCGCACTGTTTATGATGAT GCTGCTAGACGTGTTTGGACACTGATGAATGTCATTACACTTGTTTACAAAGTCTACTATGGTAATGCTTT AGATCAAGCTATTTCCATGTGGGCCTTAGTTATTTCTGTAACCTCTAACTATTCTGGTGTCGTTACGACTA ACCTTACAGTGTATCATGCTTGTTTATTGTTTCTTAGGCTATTGTTGCTGCTGCTACTTTGGCCTTTTCTG TTTACTCAACCGTTACTTCAGGCTTACTCTTGGTGTTTATGACTACTTGGTCTCTACACAAGAATTTAGGT ATATGAACTCCCAGGGGCTTTTGCCTCCTAAGAGTAGTATTGATGCTTTCAAGCTTAACATTAAGTTGTTG GGTATTGGAGGTAAACCATGTATCAAGGTTGCTACTGTACAGTCTAAAATGTCTGACGTAAAGTGCACATC TGTGGTACTGCTCTCGGTTCTTCAACAACTTAGAGTAGAGTCATCTTCTAAATTGTGGGCACAATGTGTAC **AACTCCACAATGATATTCTTCTTGCAAAAGACACAACTGAAGCTTTCGAGAAGATGGTTTCTCTTTTGTCT** GTTTTGCTATCCATGCAGGGTGCTGTAGACATTAATAGGTTGTGCGAGGAAATGCTCGATAACCGTGCTAC TCTTCAGGCTATTGCTTCAGAATTTAGTTCTTTACCATCATATGCCGCTTATGCCACTGCCCAGGAGGCCT ATGAGCAGGCTGTAGCTAATGGTGATTCTGAAGTCGTTCTCAAAAAGTTAAAGAAATCTTTGAATGTGGCT

AAATCTGAGTTTGACCGTGATGCTGCCATGCAACGCAAGTTGGAAAAGATGGCAGATCAGGCTATGACCCA AATGTACAAACAGGCAAGATCTGAGGACAAGAGGGCAAAAGTAACTAGTGCTATGCAAACAATGCTC**TTCA** CTATGCTTAGGAAGCTTGATAATGATGCACTTAACAACATTATCAACAATGCGCGTGATGGTTGTGTTCCA CTCAACATCATACCATTGACTACAGCAGCCAAACTCATGGTTGTTGTCCCTGATTATGGTACCTACAAGAA CACTTGTGATGGTAACACCTTTACATATGCATCTGCACTCTGGGAAATCCAGCAAGTTGTTGATGCGGATA GCAAGATTGTTCAACTTAGTGAAATTAACATGGACAATTCACCAAATTTGGCTTGGCCTCTTATTGTTACA GCTCTAAGAGCCAACTCAGCTGTTAAACTACAGAATAATGAACTGAGTCCAGTAGCACTACGACAGATGTC CTGTGCGGCTGGTACCACAAACAGCTTGTACTGATGACAATGCACTTGCCTACTAFAACAATTCGAAGG GAGGTAGGTTTGTGCTGGCATTACTATCAGACCACCAAGATCTCAAATGGGCTAGAT<sup>†</sup>TCCCTAAGA**GTGAT** GGTACAGGTACAATTTACACAGAACTGGAACCACCTTGTAGGTTTGTTACAGACACACCAAAAAGGGCCTAA AGTGAAATACTTGTACTTCATCAAAGGCTTAAACAACCTAAATAGAGGTATGGTGCTGGGCAGT**TTAGCTG** CTACAGTACGTCTTCAGGCTGGAAATGCTACAGAAGTACCTGCCAATTCAACTGTGCTTTCCTTCTGTGCT TTTGCAGTAGACCCTGCTAAAGCATATAAGGATTACCTAGCAAGTGGAGGACAACCAATCACCAACTGTGT GAAGATGTTGTGTACACACACTGGTACAGGACAGGCAATTACTGTAACACCAGAAGCTAACATGGACC**AAG** AGTCCTTTGGTGGTGCTTCATGTTGTCTGTATTGTAGATGCCACATTGACCATCCAAATCCTAAAGGATTC TGTGACTTGAAAGGTAAGTACGTCCAAATACCTACCACTTGTGCTAATGACCCAGTGGGTTTTACACTTAG AAACACAGTCTGTACCGTCTGCGGAATGTGGAAAGGTTATGGCTGTAGTTGTGACCAACTCCGCGAACCCT TGATGCAGTCTGCGGATGCATCAACGTTTTTAAACGGGTTTTGCGGTGTAAGTGCAGCCCGTCTTACACCGT GCGGCACAGGCACTAGTACTGATGTCGTCTACAGGGCTTTTGATATTTACAACGAAAAAGTTGCTGG**TTTT** GCAAAGTTCCTAAAAACTAATTGCTGTCGCTTCCAGGAGAAGGATGAGGAAGGCAATTTATTAGACTCTTA CTTTGTAGTTAAGAGGCATACTATGTCTAACTACCAACATGAAGAGACTATTTATAACTTGGTTAAA**GATT** GTCCAGCGGTTGCTGCCATGACTTTTTCAAGTTTAGAGTAGATGGTGACATGGTACCACATATATCACGT CAGCGTCTAACTAAATACACAATGGCTGATTTAGTCTATGCTCTACGTCATTTTGATGAGGGTAATTGTGA TACATTAAAAGAAATACTCGTCACATACAATTGCTGTGATGATGATTATTTCAATAAGAAGGATTGGTATG ACTTCGTAGAGAATCCTGACATCTTACGCGTATATGCTAACTTAGGTGAGCGTGTACGCCAATCATTATTA AAGACTGTACAATTCTGCGATGCTATGCGTGATGCAGGCATTGTAGGCGTACTGACATTAGATAATCAGGA TCTTAATGGGAACTGGTACGATTTCGGTGATTTCGTACAAGTAGCACCAGGCTGCGGAGTTCCTATTGTGG ATTCATATTACTCATTGCTGATGCCCATCCTCACTTTGACTAGGGCATTGGCTGCTGAGTCCCATATGGAT GCTGATCTCGCAAAACCACTTATTAAGTGGGATTTGCTGAAATATGATTTTACGGAAGAGAGACTTT**GTCT** CTTCGACCGTTATTTTAAATATTGGGACCAGACATACCATCCCAATTGTATTAACTGTTTGGATGATAGGT GTATCCTTCATTGTGCAAACTTTAATGTGTTATTTTCTACTGTGTTTCCACCTACAAGTTTTGGACCACTA GTAAGAAAATATTTGTAGATGGTGTTCCTTTTGTTGTTCAACTGGATACCATTTTCGTGAGTTAGGAGT CGTACATAATCAGGATGTAAACTTACATAGCTCGCGTCTCAGTTTCAAGGAACTTTTAGTGTATGCTGCTGCTG ATCCAGCTATGCATGCAGCTTCTGGCAATTTATTGCTAGATAAACGCACTACATGCTTTTCAGTAGCTGCA CTAACAAACAATGTTGCTTTTCAAACTGTCAAACCGGTAATTTTAATAAAGACTTTTATGACTTTGCTGT GTCTAAAGGTTTCTTTAAGGAAGGAAGTTCTGTTGAACTAAAACACTTCTTCTTTGCTCAGGATGGCAACG CTGCTATCAGTGATTATGACTATTATCGTTATAATCTGCCAACAATGTGTGATATCAGACAACTCCTA**TT**C TAACAATCTGGATAAATCAGCTGGTTTCCCATTTAATAAATGGGGTAAGGCTAGACTTTATTATGACTCAA TGAGTTATGAGGATCAAGATGCACTTTTCGCGTATACTAAGCGTAATGTCATCCCTACTATAACTCAAATG AATCTTAAGTATGCCATTAGTGCAAAGAATAGAGCTCGCACCGTAGCTGGTGTCTCTATCTGTAGTACTAT GACAAATAGACAGTTTCATCAGAAATTATTGAAGTCAATAGCCGCCACTAGAGGAGCTACTGTGGTAATTG GAACAAGCAAGTTTTACGGTGGCTGGCATAATATGTTAAAAACTGTTTACAGTGATGTAGAAACTCCA**CA**C CTTATGGGTTGGGATTATCCAAAATGTGACAGAGCCATGCCTAACATGCTTAGGATAATGGCCTCTCT**TG**T TCTTGCTCGCAAACATAACACTTGCTGTAACTTATCACACCGTTTCTACAGGTTAGCTAACGAGTGTGCGC AAGTATTAAGTGAGATGGTCATGTGTGGCGGCTCACTATATGTTAAACCAGGTGGAACATCATCCGGTGAT GCTACAACTGCTTATGCTAATAGTGTCTTTAACATTTGTCAAGCTGTTACAGCCAATGTAAATGCACTTCT TTCAACTGATGGTAATAAGATAGCTGACAAGTATGTCCGCAATCTACAACACAGGCTCTATGAGTGTC**TCT** ATAGAAATAGGGATGTTGATCATGAATTCGTGGATGAGTTTTACGCTTACCTGCGTAAACATTTCTCCATG TAAGAACTTTAAGGCAGTTCTTTATTATCAAAATAATGTGTTCATGTCTGAGGCAAAATGTTGGACTGAGA CTGACCTTACTAAAGGACCTCACGAATTTTGCTCACAGCATACAATGCTAGTTAAACAAGGAGATGATTAC GTGTACCTGCCTTACCCAGATCCATCAAGAATATTAGGCGCAGGCTGTTTTGTCGATGATATTGTCAAAAC AGATGGTACACTTATGATTGAAAGGTTCGTGTCACTGGCTATTGATGCTTACCACTTACAAAACATCCTA ATCAGGAGTATGCTGATGTCTTTCACTTGTATTTACAATACATTAGAAAGTTACATGATGAGCTTACTGGC CACATGTTGGACATGTATTCCGTAATGCTAACTAATGATAACACCTCACGGTACTGGGAACCTGAGTTT**TA** TGAGGCTATGTACACACACATACAGTCTTGCAGGCTGTAGGTGCTTGTGTATTGTGCAATTCACAGACTT

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CACTTCGTTGCGGTGCCTGTATTAGGAGACCATTCCTATGTTGCAAGTGCTGCTATGACCATGTCATTTCA ACATCACACAAATTAGTGTTGTCTGTTAATCCCTATGTTTGCAATGCCCCAGGTTGTGATGTCACTGATGT GACACAACTGTATCTAGGAGGTATGAGCTATTATTGCAAGTCACATAAGCCTCCCATTAGTTTTCCATTAT GTGCTAATGGTCAGGTTTTTGGTTTATACAAAAACACATGTGTAGGCAGTGACAATGTCACTGACTTCAAT GCGATAGCAACATGTGATTGGACTAATGCTGGCGATTACATACTTGCCAACACTTGTACTGAGAGACTCAA GCTTTTCGCAGCAGAAACGCTCAAAGCCACTGAGGAAACATTTAAGCTGTCATATGGTATTGCCACTGTAC GCGAAGTACTCTCTGACAGAGAATTGCATCTTTCATGGGAGGTTGGAAAACCTAGACCACCATTGAACAGA AACTATGTCTTTACTGGTTACCGTGTAACTAAAAATAGTAAAGTACAGATTGGAGAGTACACCTTTGAAAA. AGGTGACTATGGTGATGCTGTTGTGTACAGAGGTACTACGACATACAAGTTGAATGTTGGTGATTACTTTG TGTTGACATCTCACACTGTAATGCCACTTAGTGCACCTACTCTAGTGCCACAAGAGCACTATGTGAGAATT ACTGGCTTGTACCCAACACTCAACATCTCAGATGAGTTTTCTAGCAATGTTGCAAATTATCAAAAGGTCGG CATGCAAAAGTACTCTACACTCCAAGGACCACCTGGTACTGGTAAGAGTCATTTTGCCATCGGACTTGCTC TCTATTACCCATCTGCTCGCATAGTGTATACGGCATGCTCTCATGCAGCTGTTGATGCCCTATGTGAAAAAG GCATTAAAATATTTGCCCATAGATAAATGTAGTAGAATCATACCTGCGCGTGCGCGCGTAGAGTGTTTTGA TAAATTCAAAGTGAATTCAACACTAGAACAGTATGTTTTCTGCACTGTAAATGCATTGCCAGAAACAACTG CTGACATTGTAGTCTTTGATGAAATCTCTATGGCTACTAATTATGACTTGAGTGTTGTCAATGCTAGACTT CGTGCAAAACACTACGTCTATATTGGCGATCCTGCTCAATTACCAGCCCCCCGCACATTGCTGACTAAAGG CACACTAGAACCAGAATATTTTAATTCAGTGTGCAGACTTATGAAAACAATAGGTCCAGACATGTTCCTTG GAACTTGTCGCCGTTGTCCTGCTGAAATTGTTGACACTGTGAGTGCTTTAGTTATGACAATAAGCTAAAA GCACACAAGGATAAGTCAGCTCAATGCTTCAAAATGTTCTACAAAGGTGTTATTACACATGATGTTTCATC TGCAATCAACAGACCTCAAATAGGCGTTGTAAGAGAATTTCTTACACGCAATCCTGCTTGGAGAAAAGCTG TTTTTATCTCACCTTATAATTCACAGAACGCTGTAGCTTCAAAAATCTTAGGATTGCCTACGCAGACTGTT GATTCATCACAGGGTTCTGAATATGACTATGTCATATTCACACAAACTACTGAAACAGCACACACTCTTGTAA TGTCAACCGCTTCAATGTGGCTATCACAAGGGCAAAAATTGGCATTTTGTGCATAATGTCTGATAGAGATC TTTATGACAAACTGCAATTTACAAGTCTAGAAATACCACGTCGCAATGTGGCTACATTACAAGCAGAAAAT GTAACTGGACTTTTTAAGGACTGTAGTAAGATCATTACTGGTCTTCATCCTACACAGGCACCTACACACCT  ${\tt CAGCGTTGATATAAAGTTCAAGACTGAAGGATTATGTGTTGACATACCAGGCATACCAAAGGACATGACCT}$ ACCGTAGACTCATCTCTATGATGGGTTTCAAAATGAATTACCAAGTCAATGGTTACCCTAATATGTTTATC ACCCGCGAAGAAGCTATTCGTCACGTTCGTGCGTGGATTGGCTTTGATGTAGAGGGCTGTCATGCAACTAG AGATGCTGTGGGTACTAACCTACCTCTCCAGCTAGGATTTTCTACAGGTGTTAACTTAGTAGCTGTACCGA CTGGTTATGTTGACACTGAAAATAACACAGAATTCACCAGAGTTAATGCAAAACCTCCACCAGGTGACCAG TTTAAACATCTTATACCACTCATGTATAAAGGCTTGCCCTGGAATGTAGTGCGTATTAAGATAGTACAAAT GCTCAGTGATACACTGAAAGGATTGTCAGACAGAGTCGTGTTCGTCCTTTTGGGCCGCATGGCTTTGAGCTTA CATCAATGAAGTACTTTGTCAAGATTGGACCTGAAAGAACGTGTTGTCTGTGACAAACGTGCAACTTGC TATGATTGATGTTCAGCAGTGGGGCTTTACGGGTAACCTTCAGAGTAACCATGACCAACATTGCCAGGTAC ATGGAAATGCACATGTGGCTAGTTGTGATGCTATCATGACTAGATGTTTAGCAGTCCATGAGTGCTTTGTT AAGCGCGTTGATTGGTCTGTTGAATACCCTATTATAGGAGATGAACTGAGGGTTAATTCTGCTTGCAGAAA AGTACAACACATGGTTGTGAAGTCTGCATTGCTTGCTGATAAGTTTCCAGTTCTTCATGACATTGGAAAATC CAAAGGCTATCAAGTGTGTGCCTCAGGCTGAAGTAGAATGGAAGTTCTACGATGCTCAGCCATGTAGTGAC AAAGCTTACAAAATAGAGGAACTCTTCTATTCTTATGCTACACATCACGATAAATTCACTGATGGTGTTTG TTTGTTTTGGAATTGTAACGTTGATCGTTACCCAGCCAATGCAATTGTGTGTAGGTTTGACACAAGAGTCT GTCTCATGGCAAACAAGTAGTGTCGGATATTGATTATGTTCCACTCAAATCTGCTACGTGTATTACACGAT GCAATTTAGGTGGTGCTGTTTGCAGACACCATGCAAATGAGTACCGACAGTACTTGGATGCATATAATATG ATGATTTCTGCTGGATTTAGCCTATGGATTTACAAACAATTTGATACTTATAACCTGTGGAATACATTTAC CAGGTTACAGAGTTTAGAAAATGTGGCTTATAATGTTGTTAATAAAGGACACTTTGATGGACACGCCGCCG AAGCACCTGTTTCCATCATTAATAATGCTGTTTACACAAAGGTAGATGGTATTGATGTGGAGATCTTTGAA AATAAGACAACACTTCCTGTTAATGTTGCATTTGAGCTTTGGGCTAAGCGTAACATTAAACCAGTGCCAGA

ACATCGTTTATGGAGATTTCAGTCATGGACAACTTGGCGGTCTTCATTTAATGATAGGCTTAGCCAAGCGC TCACAAGATTCACCACTTAAATTAGAGGATTTTATCCCTATGGACAGCACAGTGAAAAATTACTTCATA**AC** TAATAAAGTCACAAGATTTGTCAGTGATTTCAAAAGTGGTCAAGGTTACAATTGACTATGCTGAAATTTCA ACCAGGTGTTGCGATGCCTAACTTGTACAAGATGCAAAGAATGCTTCTTGAAAAGTGTGACCTTCAGAATT ATGGTGAAAATGCTGTTATACCAAAAGGAATAATGATGAATGTCGCAAAGTATACTCAACTGTGTCAATAC TTAAATACACTTACTTTAGCTGTACCCTACAACATGAGAGTTATTCACTTTGGTGCTGGCTCTGATAAAGG AGTTGCACCAGGTACAGCTGTGCTCAGACAATGGTTGCCAACTGGCACACTACTTGTCGATTCAGATCTTA ATGACTTCGTCTCCGACGCAGATTCTACTTTAATTGGAGACTGTGCAACAGTACATACGGCTAATAAATGG GACCTTATTATTAGCGATATGTATGACCCTAGGACCAAACATGTGACAAAAGAGAATGACTCTAAAGAAGAGA GTTTTTCACTTATCTGTGTGGATTTATAAAGCAAAAACTAGCCCTGGGTGGTTCTATAGCTGTAAAGATAA CAGAGCATTCTTGGAATGCTGACCTTTACAAGCTTATGGGCCATTTCTCATGGTGGACAGCTTTTGTTACA AATGTAAATGCATCATCAGGAAGCATTTTTAATTGGGGCTAACTATCTTGGCAAGCCGAAGGAACAAAT  $\tt TGATGGCTATACCATGCTAACTACATTTTCTGGAGGAACACAAATCCTATCCAGTTGTCTTCCTATT$ CACTCTTTGACATGAGCAAATTTCCTCTTAAATTAAGAGGAACTGCTGTAATGTCTCTTAAGGAGAATCAA ATCAATGATATGATTTATTCTCTTCTGGAAAAAGGTAGGCTTATCATTAGAGAAAACAACAGAGTTGTGGT GTAGTGACCTTGACCGGTGCACCACTTTTGATGATGTTCAAGCTCCTAATTACACTCAACATACTTCATCT TCCATTTTATTCTAATGTTACAGGGTTTCATACTATTAATCATACGTTTGGCAACCCTGTCATACCTTTTA AGGATGGTATTTATTTTGCTGCCACAGAGAAATCAAATGTTGTCCGTGGTTGGGTTTTTGGTTCTACCATG AACAACAAGTCACAGTCGGTGATTATTATTAACAATTCTACTAATGTTGTTATACGAGCATGTAACTTTGA ATTGTGTGACAACCCTTTCTTTGCTGTTTCTAAACCCATGGGTACACAGACACATACTATGATATTCGATA ATGCATTTAATTGCACTTTCGAGTACATATCTGATGCCTTTTCGCTTGATGTTTCAGAAAAGTCAGGTAAT TTTAAACACTTACGAGAGTTTGTGTTTAAAAATAAAGATGGGTTTCTCTATGTTTATAAGGGCTATCAACC TATAGATGTAGTTCGTGATCTACCTTCTGGTTTTAACACTTTGAAACCTATTTTAAGTTGCCTCTTGGTA TTAACATTACAAATTTTAGAGCCATTCTTACAGCCTTTTCACCTGCTCAAGACATTTGGGGCACGTCAGCT GCAGCCTATTTTGTTGGCTATTTAAAGCCAACTACATTTATGCTCAAGTATGATGAAAATGGTACAATCAC AAGGAATTTACCAGACCTCTAATTTCAGGGTTGTTCCCTCAGGAGATGTTGTGAGATTCCCTAATATTACA AACTTGTGTCCTTTTGGAGAGGTTTTTAATGCTACTAAATTCCCTTCTGTCTATGCATGGGAGAAAAAA **AATTTCTAATTGTGTTGCTGATTACTCTGTGCTCTACAACTCAACATTTTTTTCAACCTTTAAGTGCTATG** GCGTTTCTGCCACTAAGTTGAATGATCTTTGCTTCTCCAATGTCTATGCAGATTCTTTTGTAGTCAAGGGA GATGATGTAAGACAAATAGCGCCAGGACAAACTGGTGTTATTGCTGATTATAATTATAAATTGCCAGATGA TTTCATGGGTTGTCTTGCTTGGAATACTAGGAACATTGATGCTACTTCAACTGGTAATTATAATTATA AATATAGGTATCTTAGACATGGCAAGCTTAGGCCCTTTGAGAGACATATCTAATGTGCCTTTCTCCCCT GATGGCAAACCTTGCACCCCACCTGCTCTTAATTGTTATTGGCCATTAAATGATTATGGTTTTTACACCAC TTTGTGGACCAAAATTATCCACTGACCTTATTAAGAACCAGTGTGTCAATTTTAATTTTAATGGACTCACT GGTACTGGTGTTTAACTCCTTCTTCAAAGAGATTTCAACCATTTCAACAATTTGGCCGTGATGTTTCTGA TTTCACTGATTCCGTTCGAGATCCTAAAACATCTGAAATATTAGACATTTCACCTTGCGCTTTTGGGGGGTG TAAGTGTAATTACACCTGGAACAAATGCTTCATCTGAAGTTGCTGTTCTATATCAAGATGTTAACTGCACT GATGTTTCTACAGCAATTCATGCAGATCAACTCACACCAGCTTGGCGCATATATTCTACTGGAAACAATGT ATTCCAGACTCAAGCAGGCTGTCTTATAGGAGCTGAGCATGTCGACACTTCTTATGAGTGCGACATTCCTA TTGGAGCTGGCATTTGTGCTAGTTACCATACAGTTTCTTTATTACGTAGTACTAGCCAAAAATCTATTGTG GCTTATACTATGTCTTTAGGTGCTGATAGTTCAATTGCTTACTCTAATAACACCATTGCTATACCTACTAA  $\verb|CTTTTCAATTAGCATTACTACAGAAGTAATGCCTGTTTCTATGGCTAAAACCTCCGTAGATTGTAATATGT| \\$ GTACAAAACCCCAACTTTGAAATATTTTGGTGGTTTTAATTTTTCACAAATATTACCTGACCCTCTAAAGC CAACTAAGAGGTCTTTTATTGAGGACTTGCTCTTTAATAAGGTGACACTCGCTGATGCTGCTTCATGAAG CAATATGGCGAATGCCTAGGTGATATTAATGCTAGAGATCTCATTTGTGCGCAGAAGTTCAATGGACTTAC CTGCTGGATGGACATTTGGTGCTGCCGCTCCTCTAAATACCTTTTGCTATGCAAATGGCATATAGGTTC GATTAGTCAAATTCAAGAATCACTTACAACAACATCAACTGCATTGGGCAAGCTGCAAGACGTTGTTAACC

AGAATGCTCAAGCATTAAACACACTTGTTAAACAACTTAGCTCTAATTTTGGTGCAATTTCAAGTGTGCTA AATGATATCCTTTCGCGACTTGATAAAGTCGAGGCGGAGGTACAAATTGACAGGTTAATTACAGGCAGACT TCAAAGCCTTCAAACCTATGTAACACAACAACTAATCAGGGCTGCTGAAATCAGGGCTTCTGCTAATCTTG CTGCTACTAAAATGTCTGAGTGTGTTCTTGGACAATCAAAAAGAGTTGACTTTTGTGGAAAGGGCTACCAC CTTATGTCCTTCCCACAAGCAGCCCCGCATGGTGTTGTCTTCCTACATGTCACGTATGTGCCATCCCAGGA GAGGAACTTCACCACAGCGCCAGCAATTTGTCATGAAGGCAAAGCATACTTCCCTCGTGAAGGTGTTTTTG TGTTTAATGGCACTTCTTGGTTTATTACACAGAGGAACTTCTTTTCTCCACAAATAATTACTACAGACAAT ACATTTGTCTCAGGAAATTGTGATGTCGTTATTGGCATCATTAACAACACAGTTTATGATCCTCTGCAACC TGAGCTTGACTCATTCAAAGAAGAGCTGGACAAGTACTTCAAAAAATCATACATCACCAGATGTTGATCTTG GCGACATTTCAGGCATTAACGCTTCTGTCGTCAACATTCAAAAAGAAATTGACCGCCTCAATGAGGTCGCT AAAAATTTAAATGAATCACTCATTGACCTTCAAGAATTGGGAAAATATGAGCAATATATTAAATGGCCT**TG** GTATGTTTGGCTCGGCTTCATTGCTGGACTAATTGCCATCGTCATGGTTACAATCTTGCTTTGTTGCATGA CTAGTTGTTGCAGTTGCCTCAAGGGTGCATGCTCTTGTGGTTCTTGCTGCAAGTTTGATGAGGATGACTCT GAGCCAGTTCTCAAGGGTGTCAAATTACATTACACATAAACGAACTTATGGATTTGTTTATGAGATTTTTT ACTCTTAGATCAATTACTGCACAGCCAGTAAAAATTGACAATGCTTCTCCTGCAAGTACTGTTCATGCTAC AGCAACGATACCGCTACAAGCCTCACTCCCTTTCGGATGGCTTGTTATTGGCGTTGCATTTCTTGCTGTTT TTCAGAGCGCTACCAAAATAATTGCGCTCAATAAAAGATGGCAGCTAGCCCTTTATAAGGGCTTCCAGTTC ATTTGCAATTTACTGCTGCTATTTGTTACCATCTATTCACATCTTTTGCTTGTCGCTGCAGGTATGGAGGC GCAATTTTTGTACCTCTATGCCTTGATATATTTTCTACAATGCATCAACGCATGTAGAATTATTATGAGAT ACACATAACTATGACTACTGTATACCATATAACAGTGTCACAGATACAATTGTCGTTACTGAAGGTGACGG CATTTCAACACCAAAACTCAAAGAAGACTACCAAATTGGTGGTTATTCTGAGGATAGGCACTCAGGTGTTA AAGACTATGTCGTTGTACATGGCTATTTCACCGAAGTTTACTACCAGCTTGAGTCTACACAAATTACTACA GACACTGGTATTGAAAATGCTACATTCTTCATCTTTAACAAGCTTGTTAAAGACCCACCGAATGTGCAAAT ACACACAATCGACGCTCTTCAGGAGTTGCTAATCCAGCAATGGATCCAATTTATGATGAGCCGACGACGA CTACTAGCGTGCCTTTGTAAGCACAAGAAAGTGAGTACGAACTTATGTACTCATTCGTTTCGGAAGAAACA GGTACGTTAATAGTTAATAGCGTACTTCTTTTTCTTGCTTTCGTGGTATTCTTGCTAGTCACACTAGCCAT ACGTCTACTCGCGTGTTAAAAATCTGAACTCTTCTGAAGGAGTTCCTGATCTTCTGGTCTAAACGAACTAA CTATTATTATTATTCTGTTTGGAACTTTAACATTGCTTATCATGGCAGACAACGGTACTATTACCGTTGAG GAGCTTAAACAACTCCTGGAACAATGGAACCTAGTAATAGGTTTCCTAGTCCTAGCCTGGATTATGTTACT ACAATTTGCCTATTCTAATCGGAACAGGTTTTTGTACATAATAAAGCTTGTTTTCCTCTGGCTCTTGTGGC CCGCTCAATGTGGTCATTCAACCCAGAAACAAACATTCTTCTCAATGTGCCTCTCCGGGGGACAATTGTGA CCAGACCGCTCATGGAAAGTGAACTTGTCATTGGTGCTGTGATCATTCGTGGTCACTTGCGAATGGCCGGA CACTCCCTAGGGCGCTGTGACATTAAGGACCTGCCAAAAGAGATCACTGTGGCTACATCACGAACGCTTTC TTATTACAAATTAGGAGCGTCGCAGCGTGTAGGCACTGATTCAGGTTTTGCTGCATACAACCGCTACCGTA TTGGAAACTATAAATTAAATACAGACCACGCCGGTAGCAACGACAATATTGCTTTGCTAGTACAGTAAGTG ACAACAGATGTTTCATCTTGTTGACTTCCAGGTTACAATAGCAGAGATATTGATTATCATTATGAGGACTT TCAGGATTGCTATTTGGAATCTTGACGTTATAATAAGTTCAATAGTGAGACAATTATTTAAGCCTCTAACT AAGAAGAATTATTCGGAGTTAGATGATGAAGAACCTATGGAGTTAGATTATCCATAAAACGAACATGAAAA ACGACTGTACTACAAAAGAACCTTGCCCATCAGGAACATACGAGGGCAATTCACCATTTCACCCTCTTGC TGACAATAAATTTGCACTAACTTGCACTAGCACACACTTTGCTTTTGCTTGTGCTGACGGTACTCGACATA CCTATCAGCTGCGTGCAAGATCAGTTTCACCAAAACTTTTCATCAGACAAGAGGGGGTTCAACAAGAGCTC TACTCGCCACTTTTTCTCATTGTTGCTGCTCTAGTATTTTTAATACTTTGCTTCACCATTAAGAGAAAGAC AGAATGAATGAGCTCACTTTAATTGACTTCTATTTGTGCTTTTTAGCCTTTCTGCTATTCCTTGTTTTAAT AATGCTTATTATATTTTGGTTTTCACTCGAAATCCAGGATCTAGAAGAACCTTGTACCAAAGTCTAAACGA ACATGAAACTTCTCATTGTTTTGACTTGTATTTCTCTATGCAGTTGCATATGCACTGTAGTACAGCGCTGT GCATCTAATAAACCTCATGTGCTTGAAGATCCTTGTAAGGTACAACACTAGGGGTAATACTTATAGCACTG CTTGGCTTTGTGCTCTAGGAAAGGTTTTACCTTTTCATAGATGGCACACTATGGTTCAAACATGCACACCT **AATGTTACTATCAACTGTCAAGATCCAGCTGGTGGTGCGCTTATAGCTAGGTGTTGGTACCTTCATGAAGG** GGACCCCAATCAAACCAACGTAGTGCCCCCCGCATTACATTTGGTGGACCCACAGATTCAACTGACAATAA CCAGAATGGAGGACGCAATGGGGCAAGGCCAAAACAGCGCCGACCCCAAGGTTTACCCAATAATACTGCGT CTTGGTTCACAGCTCTCACTCAGCATGGCAAGGAGGAACTTAGATTCCCTCGAGGCCAGGGCGTTCCAATC

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AACACCAATAGTGGTCCAGATGACCAAATTGGCTACTACCGAAGAGCTACCCGACGAGTTCGTGGTGGTGA CGGCAAAATGAAAGAGCTCAGCCCCAGATGGTACTTCTATTACCTAGGAACTGGCCCAGAAGCTTCACTTC CCTACGGCGCTAACAAGAAGGCATCGTATGGGTTGCAACTGAGGGGAGCCTTGAATACACCCAAAGACCAC ATTGGCACCCGCAATCCTAATAACAATGCTGCCACCGTGCTACAACTTCCTCAAGGAACAACATTGCCAAA AGGCTTCTACGCAGAGGGAAGCAGAGGCGGCAGTCAAGCCTCTTCTCGCTCCTCATCACGTAGTCGCGGTA ATTCAAGAAATTCAACTCCTGGCAGCAGTAGGGGAAATTCTCCTGCTCGAATGGCTAGCGGAGGTGGTGAA ACTGCCCTCGCGCTATTGCTGCTAGACAGATTGAACCAGCTTGAGAGCAAAGTTTCTGGTAAAGGCCAACA ACAACAAGGCCAAACTGTCACTAAGAAATCTGCTGCTGAGGCATCTAAAAAGCCTCQCCAAAAACGTACTG CCACAAAACAGTACAACGTCACTCAAGCATTTGGGAGACGTGGTCCAGAACAAACCCAAGGAAATTTCGGG GACCAAGACCTAATCAGACAAGGAACTGATTACAAACATTGGCCGCAAATTGCACAATTTGCTCCAAGTGC CTCTGCATTCTTTGGAATGTCACGCATTGGCATGGAAGTCACACCTTCGGGAACATGGCTGACTTATCATG GAGCCATTAAATTGGATGACAAAGATCCACAATTCAAAGACAACGTCATACTGCTGAACAAGCACATTGAC GCATACAAAACATTCCCACCAACAGAGCCTAAAAAGGACAAAAAGAAAAAGACTGATGAAGCTCAGCCTTT GCCGCAGAGACAAAAGAAGCAGCCCACTGTGACTCTTCTTCCTGCGGCTGACATGGATGATTTCTCCAGAC AACTTCAAAATTCCATGAGTGGAGCTTCTGCTGATTCAACTCAGGCATAAACACTCATGATGACCACACAA TCTCGTAACTAAACAGCACAAGTAGGTTTAGTTAACTTTAATCTCACATAGCAATCTTTAATCAATGTGTA ACATTAGGGAGGACTTGAAAGAGCCACCACATTTTCATCGAGGCCACGCGGAGTACGATCGAGGGTACAGT 

GenBank Accession No. AY274119.2.; SEQ ID NO: 2

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ERV-2	
TOR2	A CARONICA DOS COS CASOS CASOS CONTROLOGOS A
	ACACTCATGATGACCACACAAGGCAGATGGGCTATGTAAACGTTTTCGCAATTCCGTTTA
AI <b>BV</b>	
9	
ERV-2	
TOR2	CGATACATAGTCTACTCTTGTGCAGAATGAATTCTCGTAACTAAACAGCACAAGTAGGTT
AIBV	Control of the Contro
VIDA	
<u>.</u> •	
ERV-2	
TOR2	TAGTTAACTTTAATCTCACATAGCAATCTTTAATCAATGTGTAACATTAGGGAGGACTTG
AIBV	TAGTTTAGTTTAG
	* * ** *
ERV-2	CCTTTCTCACTCGCCGAGGCCACGCGAGTAGGACCGAGGGTACAGC
	•
TOR2	AAAGAGCCACCATTTTCATCGAGGCCACGCGAGTTACGATCGAGGGTACAGT
AIBV	AGTAGGTATAAAGATGCCAGTGCCGGGGCCACGCGGAGTACGATCGAGGGTACAGCACTA
	* ** ****** ** *******
ERV-2	-GAGTCTTT-TAGTTTAAGGTGT-TAGATGTAAGGTACGTGGGCTTTCTTTTGGTTTA
TOR2	-GAATAATGCTAGGGAGAGCTGCCTATATGGAAGAGCCCTAATGTGTAAAATTAATT
AIBV	GGACGCCATTAGGGGAAGA-GCTAAATTTTAGTTTAAGTTTAAGTTTAAATTGGCTAA
NTD4	*** ** * * * * * * * * * * * * * * * *
ERV-2	CTTCTTC GenBank: AF361253 (SEQ ID NO: 31)
TOR2	GTAGTGCTATCCCCATGTGATTTTAATAGCTTCTTAGGAGAATGAC (SEQ ID NO: 18)
AIBV	GTATAGTTAAAATTTATAGGCTAGTATAGAGTTAGAGCA GenBank: NC 001451 (SEO ID NO: 32)

Figure 4

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MFIFLLFLTLTSGSDLDRCTTFDDVQAPNYTQHTSSMRGVYYPDEIFRSD TLYLTODLFLPFYSNVTGFHTINHTFGNPVIPFKDGIYFAATEKSNVVRG WVFGSTMNNKSQSVIIINNSTNVVIRACNFELCDNPFFAVSKPMGTQTHT MIFDNAFNCTFEYISDAFSLDVSEKSGNFKHLREFVFKNKDGFLYVYKGY QPIDVVRDLPSGFNTLKPIFKLPLGINITNFRAILTAFSPAQDIWGTSAA AYFVGYLKPTTFMLKYDENGTITDAVDCSQNPLAELKCSVKSFEIDKGIY QTSNFRVVPSGDVVRFPNITNLCPFGEVFNATKFPSVYAWERKKISNCVA DYSVLYNSTFFSTFKCYGVSATKLNDLCFSNVYADSFVVKGDDVRQIAPG QTGVIADYNYKLPDDFMGCVLAWNTRNIDATSTGNYNYKYRYLRHGKLRP FERDISNVPFSPDGKPCTPPALNCYWPLNDYGFYTTTGIGYQPYRVVVLS FELLNAPATVCGPKLSTDLIKNQCVNFNFNGLTGTGVLTPSSKRFQPFQQ FGRDVSDFTDSVRDPKTSEILDISPCAFGGVSVITPGTNASSEVAVLYQD VNCTDVSTAIHADQLTPAWRIYSTGNNVFQTQAGCLIGAEHVDTSYECDI PIGAGICASYHTVSLLRSTSQKSIVAYTMSLGADSSIAYSNNTIAIPTNF SISITTEVMPVSMAKTSVDCNMYICGDSTECANLLLQYGSFCTQLNRALS GIAAEQDRNTREVFAQVKQMYKTPTLKYFGGFNFSQILPDPLKPTKRSFI EDLLFNKVTLADAGFMKQYGECLGDINARDLICAQKFNGLTVLPPLLTDD MIAAYTAALVSGTATAGWTFGAGAALOIPFAMOMAYRFNGIGVTQNVLYE NOKQIANQFNKAISQIQESLTTTSTALGKLQDVVNQNAQALNTLVKQLSS NFGAISSVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEI RASANLAATKMSECVLGOSKRVDFCGKGYHLMSFPQAAPHGVVFLHVTYV PSOERNFTTAPAICHEGKAYFPREGVFVFNGTSWFITQRNFFSPQIITTD NTFVSGNCDVVIGIINNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGD ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYVWL GFIAGLIAIVMVTILLCCMTSCCSCLKGACSCGSCCKFDEDDSEPVLKGV (SEQ ID NO: 33)

### Figure 5

MADNGTITVEELKQLLEQWNLVIGFLFLAWIMLLQFAYSNRNRFLYIIKL VFLWLLWPVTLACFVLAAVYRINWVTGGIAIAMACIVGLMWLSYFVASFR LFARTRSMWSFNPETNILLNVPLRGTIVTRPLMESELVIGAVIIRGHLRM AGHSLGRCDIKDLPKEITVATSRTLSYYKLGASQRVGTDSGFAAYNRYRI GNYKLNTDHAGSNDNIALLV (SEQ ID NO: 34)

Figure 6

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MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVS LVKPTVYVYSRVKNLNSSEGVPDLLV (SEQ ID NO: 35)

# Figure 7

MSDNGPQSNQRSAPRITFGGPTDSTDNNQNGGRNGARPKQRRPQGLPNNT ASWFTALTQHGKEELRFPRGQGVPINTNSGPDDQIGYYRRATRRVRGGDG KMKELSPRWYFYYLGTGPEASLPYGANKEGIVWVATEGALNTPKDHIGTR NPNNNAATVLQLPQGTTLPKGFYAEGSRGGSQASSRSSSRSRGNSRNSTP GSSRGNSPARMASGGGETALALLLLDRLNQLESKVSGKGQQQQGQTVTKK SAAEASKKPRQKRTATKQYNVTQAFGRRGPEQTQGNFGDQDLIRQGTDYK HWPQIAQFAPSASAFFGMSRIGMEVTPSGTWLTYHGAIKLDDKDPQFKDN VILNKHIDAYKTFPPTEPKKDKKKKTDEAQPLPQRQKKQPTVTLLPAAD MDDFSRQLQNSMSGASADSTQA (SEQ ID NO: 36)

Figure 8

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BoCov OC43 PHEV FCV TGEV TOR2_M ORF5 AIBV2 AIBV						
BoCov	GIILLFITVILQFGYTSRSMFVYVIKMVILWLMWPLTIILTIFNCVYALNN-VY <b>LGFS</b>					
OC43	GIILLFITIILQFGYTSRSMFVYVIKMIILWIMWPLTIILTIFNCYYALNN-VYLGLS					
PCV PHBV	GIIVLFITIILQFGYTSRSMFVYVIKMVILWLMWPLTIILTIFNCVYALNN-VYLGFS SIILIVFITVLQYGRPQFSWFVYGIKMLIMWLLWPIVLALTIFNAYSEYEVSRYVMFGFS					
TGEV	SILLIVFITVLOYGRPOFSWFVYGIKMLIMWLLWPVVLALTIFNAYSEYOVSRVVMFGPS					
TOR2_M	GFLFLAWIMLLQFAYSNRNRFLYIIKLVFLWLLWFVTLACFVLAAVYRINW-VTGGIA					
ORF5	GFLFLAWIMLLQFAYSNRNRFLYIIKLVFLWLLWPVTLACFVLAAVYRINW-VTGGIA					
AIBV2	TAFLLFLTILLQYGYATRSRFIYILKMIVLWCFWPLNIAVGVISCIYPPNT-GGLVAA TAFLLFLTILLQYGYATRSRFIYILKMIVLWCFWPLNIAVGIISCIYPPNT-GGLVAA					
AIBV	::: :**: *:* :*::::* :**: : :: . * . :					
BoCov	IVFTIVAIIMWIVYFVNSIRLFIRTGSWWSFNPETNNLMCIDMK-GRMYVRPII <b>EDYHTL</b>					
OC43	IVFTIVAIIMWIVYFVNSIRIFIRTGSFWSFRPETNNLMCIDMK-GTMYVRPIIEDYHTL					
PHEV FCV	IVFTIVAIIMWVVYFVNSIRLFIRTGSWWSFNPETNNLMCIDMK-GRMYVRPII <b>EDYHTL</b> VAGAVVTFALWMMYFVRSIQLYRRTKSWWSFNPETNAILCVNAL-GRSYVLPLDGT <b>PTGV</b>					
TGEV	iagaivtfvlwimyfvrsiqlyrrtkswwsfnpetkailcvsal-grsyvlplegv <b>ptgv</b>					
TOR2_M	iamacivglmwlsyfvasfrlfartrsmwsfnpetnillnvplr-gtivtrplmegelvi					
ORF5	iamacivglmwlsyfvasfrlfartrsmwsfnpetnillnvplr-gtivtrplmeselvi					
AIBV2 AIBV	<pre>IILTVFACLSFVGYWIQSCRLFKRCRSWWSFNPESNAVGSILLTNGQQCNFAIESVPMVL IILTVFACLSFVGYWIQSFRLFKRCRSWWSFNPESNAVGSILLTNGQQCNFAIESVPMVL</pre>					
VTDA	: : . : *: *: * * *******: : : * .: :					
BoCov OC43 PHEV FCV TGEV TOR2_M ORF5 AIBV2 AIBV	TVTIIRGHLYMQGIKLGTGYSLSDLPAYVTVAKVSHLLTYKRGFLDKIGDTSGFAVY TVTIIRGHLYIQGIKLGTGYSWADLPAYMTVAKVTHLCTYKRGFLDRISDTSGFAVY TATIIRGHLYIQGIKLGTGYSLSDLPAYVTVAKVTHLCTYKRGFLDRIGDTSGFAVY TLTLLSGNLYAEGFKMAGGLTIEHLPKYVMIRTPNRTIVYTLVGKQLKATTATGWAYY TLTLLSGNLYAEGFKIAGGMNIDNLPKYVMVALPSRTIVYTLVGKKLKASSATGWAYY GAVIIRGHLRMAGHSLGR-CDIKDLPKEITVAT-SRTLSYYKLGASQRVGTDSGFAAY GAVIIRGHLRMAGHSLGR-CDIKDLPKEITVAT-SRTLSYYKLGASQRVGTDSGFAAY APIIKNGVLYCEGQWLAK-CEPDHLPKDIFVCTPDRRNIYRMVQKYTGDQSGNKKRVATF. SPIIKNGALYCEGQWLAK-CEPDHLPKDIFVCTPDRRNIYRMVQKYTGDQSGNKKRVATF	•				
VIDA	* * * * : * : * : * :					
BoCov	VKSKVGNYRLPSTQKGSGLDTALLRNNI					
OC43 PHEV	VKSKVGNYRLPSTQKGSGMDTALLRNNI VKSKVGNYRLPSTHKGSGMDTALLRNNI					
FCV	VKSKAGDYSTEARTDNLSEHEKLLHMV-					
TGEV	VKSKAGDYSTEARTDNLSEQEKILHMV-					
TOR2_M	NRYRIGNYKLNTDHAGSNDNIALLVQ					
ORF5 AIBV2	NRYRIGNYKLNTDHAGSNDNIALLVQ VYAKQSVDTGELESVPTGGSSLYT					
AIBV	VYAKOSVDTGELGSVATGGSSLYT					
Key PHEV BoCov AIBV TGEV FCV OC43 AIBV2	Name Porcine hemagglutinating encephalomyelitis virus MAL80035 40.4% (SEQ ID NO: 37 Matrix protein [Bovine coronavirus].  Membrane protein [Avian infectious bronchitis virus].  Membrane protein [Transmissible gastroenteritis virus].  MP_058427 28.5% (SEQ ID NO: 4 Membrane glycoprotein [Human coronavirus OC43].  Membrane protein [Avian infectious bronchitis virus].  AAA45462 39.1% (SEQ ID NO: 4 Membrane protein [Avian infectious bronchitis virus].  AAA83027 32.0% (SEQ ID NO: 4 Membrane protein [Avian infectious bronchitis virus].	(8) (9) (0) (1) (2)				
TOR2_M/ORF 5 Sars associated coronavirus M glycoprotein (SEQ ID NO: 34)						

Figure 9

BoCov OC43 PHEV MHV AIBV2 TCV AIBV FCV PTGV 229E TOR2_N	MSFTPGKQSS-SRASSGNRSGNGILKWADQSDQSRNVQTRGRRAQPKQTATSQQP MSFTPGKQSS-SRASSGNRSGNGILKWADQSDQVRNVQTRGRRAQPKQTATSQQP MSFTPGKQSS-SRASSGNRSGNGILKWADQSDQSRNVQTRGRRVQSKQTATSQQP MSFVPGQENAGSRSSSVNRAGNGILKKTTWADQTERGPNNQNRGRRNQPKQTATTQ-PMASGKAAGKTDAPAPVIKLGGPKPPKVGSSGN
BoCov OC43 PHEV MHV AIBV2 TCV AIBV FCV PTGV 229E TOR2_N	SGGNVVPYYSWFSGITQFQKGKEFEFAEGQGVPIAPGVPATEAKGYWYRHNRRSFKTADG SGGNVVPYYSWFSGITQFQKGKEFEFAEGQGVPIAPGVPATEAKGYWYRHNRRSFKTADG SGGTVVPYYSWFSGITQFQKGKEFEFAEGQGVPIAPGVPSTEAKGYWYRHNRRSFKTADG NSGSVVPHYSWFSGITQFQKGKEFQFAQGQGVPIANGIPASEQKGYWYRHNRRSFKTPDG AS
BoCov OC43 PHEV MHV AIBV2 TCV AIBV FCV PTGV 229E TOR2_N	NQRQLLPRWYFYYLGTGPHAKDQYGTDIDGVYWVASNQADVNTPADILDRDPSSDEAIPT NQRQLLPRWYFYYLGTGPHAKDQYGTDIDGVYWVASNQADVNTPADIVDRDPSSDEAIPT NQRQLLPRWYFYYLGTGPHAKDQYGTDIDGVYWVASNQADINTPADIVDRDPSSDEAIPT QQKQLLPRWYFYYLGTGPHAGAEYGDDIDGVVWVASQQADTKTTADIVERDPSSHEAIPT GRKPVPDAWYFYYTGTGPAADLNWGDTQDGIVWVAAKGADTKSTSNQGTRDPDKFDQYPL GRKPVPDAWYFYYTGTGPAADLNWGDTQDGIVWVAAKGADVKSRSNQGTRDPDKFDQYPL GRKPVPDAWYFYYTGTGPAADLNWGDSQDGIVWVAAKGADVKSRSNQGTRDPDKFDQYPL QRVELPERWFFYLGTGPHADAKFKAKIDGVFWVARDGAMN-KPTSLGTRG-TNNESKPL QRKELPERWFFYYLGTGPHADAKFKDKLDGVVWVAKDGAMN-KPTSLGTRG-ANNESKAL KRVDLSPKLHFYYLGTGPHADAKFRERVEGVVWVAVDGAKT-EPTGYGVRR-KNSEPEIP KMYELSPRWYFYYLGTGPEASLPYGANKEGIVWVATEGALNTPKDHIGTRNPNNNAATVL  .**: **** : *** .*** .**** .**** .**** .**** .*****
BoCov OC43 PHEV MHV AIBV2 TCV AIBV FCV PTGV 229E TOR2_N	RFPPGTVLPQGYYIEGS-GRSAPNSRSTSRASSAAGSRSRANSGNRTPTSG RFPPGTVLPQGYYIEGS-GRSAPNSRSTSRTSSRASSAGSRSRANSGNRTPTSG RFPPGTVLPQGYYIEGS-GRSAPNSRSTSRAFNRAPSAGSRSRANSGNRTSTPG RFAPGTVLPQGFYVEGS-GRSAPASRSGSRSQSRGPNNRARSSSNQRQPAST RFSDGGPDGNFRWDF-IPLKNRGRSG-RSTAASSAAASRAPSREGSRGRRSD RFSDGGPDGNFRWDF-IPLH-RGRSG-RSTAASSAASSRAPSREGSRGRRSG RFSDGGPDGNFRWDF-IPLN-RGRSG-RSTAASSAASSRAPSREGSRGRLNG KFDGK-IPPQFQLEVNR-SRNNSRSGSQSRSVSRNRSQSRGRQQSNNQ-NTTNVED KFDGK-VPGEFQLEVNQ-SRDNSRLRSQSRSRSRNRSQSRGRQQSNNK-DDSVEQ HFNQKLPNGVTVVEE-PDSRAPSRSQSRSSRSRRGSSRYQSRNPSSDRNHNSQDDIMK QLPQGTTLPKGFYAEGSRGSQASSRSSRSRRGSRNSTPGSSRGNSPARMAS-GGGETA :: * *: .*
BoCov OC43 PHEV MHV AIBV2 TCV AIBV FCV PTGV 229E TOR2_N	VTPDMADQIASLVLAKLGKDAAKP

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BoCov OC43 PHEV MHV AIBV2 TCV AIBV FCV PTGV 229E TOR2_N	NKPRQKRSPNKQCTVQQCFGKRGPNQNFGGGEMLKLGTSDPQFPI NKPRQKRSPNKQCTVQQCFGKRGPNQNFGGGEMLKLGTSDPQFPI NKPRQKRSPNKQCTVQQCFGKRGPNQNFGGGEMLKLGTSDPQFPI NKPRQKRSPNKQCTVQQCFGKRGPNQNFGGSEMLKLGTSDPQFPI CKRTIPPNYRVDQVFGPRT-KGKEGNFGDDKMNEEGIKDGRVTP CKRTVPPGYKVDQVFGPRT-KGKEGNFGDDKMNEEGIKDGRVTP CKRTVPPGYSIDKVFGPRT-KGKEGNFGDDKMNEEGIKDGRVTP NKHTWKKTAGKGDVTNFYGARSSSANFGDSDLVANGNAAKCYPC NKHTWKRTAGKGDVTRFYGTRSNSANFGDSDLVANGSSAKHYPC QKRTATKQYNVTQAFGRRGPEQTQGNFGDQDLIRQGTDYKHWPC * : : ** * *** : ***	LAELAPTAGA LAELAPTAGA LAELAPTPSA MLNLVPSSHA MLNLVPSSHA MLNLVPSSHA LAECVPSVSS LAECVPSVSS PAELVPSTAA		
BoCov	FFFGSRLELAKVQNLSGNLDEPQKDVYELRYNGAIRFDSTLSGFF			
oc43	FFFGSRLELAKVQNLSGNPDEPQKDVYELRYNGAIRFDSTLSGFF	TIMKVLNENL		
PHEV	FFFGSRLELAKVQNLSGNPDEPQKDVYELRYNGAIRFDSTLSGFF	TIMKVLNQNL		
MHV	FFFGSKLELVKKNSGGADDPTKDVYELQYSGAIRFDSTLPGFF	TIMKVLNENL		
AIBV2	CLFGSRVTPKLQL~-DGLHLRFEFTTVVPCDDPQFDNYVKICDQCVDGVG			
TCV	CLFGSRVTPKLQPDGLHLRFEFTTVVPRDDPQFDNYVTICDQCVDGIG			
AIBV	CLFGSQVTPKLQPDGLHLTFRFTTVVSRDDPQFDNYVKICDECVDGVC			
FCV	ILFGSQWSAEEAGDQVKVTLTHNYYLPKDDAKTS			
PTGV	ILFGSYWTSKEDGDQIEVTFTHKYHLPKDDPKTG			
229E	MLFDSHIVSKESGNTVVLTFTTRVTVPKDHPHLGDN FFGMSRIGMEVTPSGTWLTYHGAIKLDDKDPQFKDN			
TOR2_N	: *	VIDDINKHI		
		•		•
BoCov	NAYQQQ-DGTMNMSPKPQRQRGQKNGQGENDNISVAAPKSRVQQNF	(IRELTAEDIS		
oc43	NAYQQQ-DGMMNMSPKPQRQRGHKNGQGENDNISVAVPKSRVQQNY	KSRELTAEDIS		•
PHEV	NAYQHQEDGMMNISPKPQRQRGQKNGQVENDNVSVAAPKSRVQQNF			
MHV	DAYQDQAGGADVVSPKPQRKRGTKQKALKGEVDNVSVAKPKSSVQRM			
AIBV2	KSRSSRPATRGNSPAPRQQRPKKEKKLKKQDDEADKALTSDEERNN			
TCV	KSRPSSRPATRGNSPAPRQQRPKKEKKPKKQDDEVDKALTSDEERNN			
AIBV	KSRSSSRPATRGTSPAPKQQRPKKEKKPKKQDDEVDKALTSDEERNNI DAYKRPSEVAKDORQRKSRSKSADKKPEELSVTLEAY			
FCV PTGV	NAYARPSEVAKEQRKRKSRSKSAERSEQEVVPDALIEN			
229E	NAFTREMQQHPLLNPSALEFNPSQTSPATAEP			
TOR2_N	DAYKTPPPTEPKKDKKKKTDEAQPLPQRQKKQPTVTLLPAADMDDI			
	.:	•		
	•			•
BoCov	LLKKMDEPFTEDTSEI			
OC43	LLKKMDEPYTEDTSEI		•	
PHEV	LLKKMDEPYTEDTSEI			
MHV	LLAQILDDGVVPDGLEDDSNV	*		
AIBV2	VINWGDAALGENEL			
TCV AIBV	VINWGDSALGENHL VINWGDSALGENEL			
FCV	MIDEVTN		•	
PTGV	MIDEVTN			
229E	IIDEVN			
TOR2_N	ASADSTQA		•	•
	•			
Key		Genbank	*%ID	
MHV	NUCLECCAPSID PROTRIN	P18446	34.38	(SEQ ID NO: 44)
BoCov	nucleocapsid protein [Bovine coronavirus].	NP_1500B3	34.48	(SEQ ID NO: 45)
AIBV	nucleocapsid protein [Avian infectious bronchitis virus].	AAK27162	28.3%	(SEQ ID NO: 46)
FCV	nucleocapsid [Feline coronavirus].	CAA74230	29.4% 28.0%	(SEQ ID NO: 47) (SEQ ID NO: 48)
PTGV 229E	nucleoprotein [porcine transmissible gastroenteritis virus]. nucleocapsid protein [Human coronavirus 229E].	AAM97563 NP_073556	24.6%	(SEQ ID NO: 49)
0C43				
	NUCLEOCAPSID PROTEIN.	P33469	33.9%	(SEQ ID NO: 50)
PHEV	NUCLEOCAPSID PROTEIN. nucleocapsid protein [porcine hemagglutinating encephalomyelitis]	AAL80036	33.3%	(SEQ ID NO: 51)
PHEV TCV TOR_N	NUCLEOCAPSID PROTEIN. nucleocapsid protein [porcine hemagglutinating encephalomyelitis] nucleocapsid protein [turkey coronavirus]. SARS associated virus nucleocapsid protein (SEQ ID NO: 36)			

ATATTAGGTTTTTACCTACCCAGGAAAAGCCAACCAACCTCGATCTCTTG TAGATCTGTTCTCTAAACGAACTTTAAAATCTGTGTAGCTGTCGCTCGGC TGCATGCCTAGTGCACCTACGCAGTATAAACAATAATAAATTTTACTGTC GTTGACAAGAAACGAGTAACTCGTCCCTCTTCTGCAGACTGCTTACGGTT TCGTCCGTGTTGCAGTCGATCATCAGCATACCTAGGTTTCGTCCGGGTGT GACCGAAAGGTAAGATGGAGAGCCTTGTTCTTGGTGTCAACGAGAAAACA CACGTCCAACTCAGTTTGCCTGTCCTTCAGGTTAGAGACGTGCTAGTGCG TGGCTTCGGGGACTCTGTGGAAGAGGCCCTATCGGAGGCACGTGAACACC TCAAAAATGGCACTTGTGGTCTAGTAGAGCTGGAAAAAGGCGTACTGCCC CAGCTTGAACAGCCCTATGTGTTCATTAAACGTTCTGATGCCTTAAGCAC CAATCACGGCCACAAGGTCGTTGAGCTGGTTGCAGAAATGGACGGCATTC AGTACGGTCGTAGCGGTATAACACTGGGAGTACTCGTGCCACATGTGGGC GAAACCCCAATTGCATACCGCAATGTTCTTCTTCGTAAGAACGGTAATAA GGGAGCCGGTGGTCATAGCTATGGCATCGATCTAAAGTCTTATGACTTAG GTGACGAGCTTGGCACTGATCCCATTGAAGATTATGAACAAAACTGGAAC ACTAAGCATGGCAGTGCACTCCGTGAACTCACTCGTGAGCTCAATGG AGGTGCAGTCACTCGCTATGTCGACAACAATTTCTGTGGCCCAGATGGGT ACCCTCTTGATTGCATCAAAGATTTTCTCGCACGCGCGGGCAAGTCAATG TGCACTCTTTCCGAACAACTTGATTACATCGAGTCGAAGAGAGGTGTCTA CTGCTGCCGTGACCATGAGCATGAAATTGCCTGGTTCACTGAGCGCTCTG ATAAGAGCTACGAGCACCAGACACCCTTCGAAATTAAGAGTGCCAAGAAA TTTGACACTTTCAAAGGGGAATGCCCAAAGTTTGTGTTTTCCTCTTAACTC AAAAGTCAAAGTCATTCAACCACGTGTTGAAAAGAAAAAGACTGAGGGTT TCATGGGGCGTATACGCTCTGTGTACCCTGTTGCATCTCCACAGGAGTGT AACAATATGCACTTGTCTACCTTGATGAAATGTAATCATTGCGATGAAGT TTCATGGCAGACGTGCGACTTTCTGAAAGCCACTTGTGAACATTGTGGCA AATGCTGTAGTGAAAATGCCATGTCCTGCCTGTCAAGACCCAGAGATTGG ACCTGAGCATAGTGTTGCAGATTATCACAACCACTCAAACATTGAAACTC GACTCCGCAAGGGAGGTAGGACTAGATGTTTTGGAGGCTGTGTTTTGCC TATGTTGGCTGCTATAATAAGCGTGCCTACTGGGTTCCTCGTGCTAGTGC TGATATTGGCTCAGGCCATACTGGCATTACTGGTGACAATGTGGAGACCT TGAATGAGGATCTCCTTGAGATACTGAGTCGTGAACGTGTTAACATTAAC ATTGTTGGCGATTTTCATTTGAATGAAGAGGTTGCCATCATTTTGGCATC TTTCTCTGCTTCTACAAGTGCCTTTATTGACACTATAAAGAGTCTTGATT ACAAGTCTTTCAAAACCATTGTTGAGTCCTGCGGTAACTATAAAGTTACC AAGGGAAAGCCCGTAAAAGGTGCTTGGAACATTGGACAACAGAGATCAGT TTTAACACCACTGTGTGTTTTCCCTCACAGGCTGCTGGTGTTATCAGAT CAATTTTTGCGCGCACACTTGATGCAGCAAACCACTCAATTCCTGATTTG CAAAGAGCAGCTGTCACCATACTTGATGGTATTTCTGAACAGTCATTACG TCTTGTCGACGCCATGGTTTATACTTCAGACCTGCTCACCAACAGTGTCA TTATTATGGCATATGTAACTGGTGGTCTTGTACAACAGACTTCTCAGTGG TTGTCTAATCTTTTGGGCACTACTGTTGAAAAACTCAGGCCTATCTTTGA ATGGATTGAGGCGAAACTTAGTGCAGGAGTTGAATTTCTCAAGGATGCTT GGGAGATTCTCAAATTTCTCATTACAGGTGTTTTTGACATCGTCAAGGGT CAAATACAGGTTGCTTCAGATAACATCAAGGATTGTGTAAAATGCTTCAT TGATGTTGTTAACAAGGCACTCGAAATGTGCATTGATCAAGTCACTATCG CTGGCGCAAAGTTGCGATCACTCAACTTAGGTGAAGTCTTCATCGCTCAA AGCAAGGGACTTTACCGTCAGTGTATACGTGGCAAGGAGCAGCTGCAACT ACTCATGCCTCTTAAGGCACCAAAAGAAGTAACCTTTCTTGAAGGTGATT CACATGACACAGTACTTACCTCTGAGGAGGTTGTTCTCAAGAACGGTGAA CTCGAAGCACTCGAGACGCCCGTTGATAGCTTCACAAATGGAGCTATCGT TGGCACACCAGTCTGTGTAAATGGCCTCATGCTCTTAGAGATTAAGGACA TTTCGCTTAAAAGGGGGTGCACCAATTAAAGGTGTAACCTTTGGAGAAGA TACTGTTTGGGAAGTTCAAGGTTACAAGAATGTGAGAATCACATTTGAGC TTGATGAACGTGTTGACAAAGTGCTTAATGAAAAGTGCTCTGTCTACACT

GTTGAATCCGGTACCGAAGTTACTGAGTTTGCATGTGTTGTAGCAGAGGC TGTTGTGAAGACTTTACAACCAGTTTCTGATCTCCTTACCAACATGGGTA TTGATCTTGATGAGTGGAGTGTAGCTACATTCTACTTATTTGATGATGCT GGTGAAGAAACTTTTCATCACGTATGTATTGTTCCTTTTACCCTCCAGA TGAGGAAGAAGAGGACGATGCAGAGTGTGAGGAAGAAGAAATTGATGAAA CCTGTGAACATGAGTACGGTACAGAGGATGATTATCAAGGTCTCCCTCTG GAATTTGGTGCCTCAGCTGAAACAGTTCGAGTTGAGGAAGAAGAAGAAGA AGACTGGCTGGATGATACTACTGAGCAATCAGAGATTGAGCCAGAACCAG AACCTACACCTGAAGAACCAGTTAATCAGTTTACTGGTTATTTAAAACTT ACTGACAATGTTGCCATTAAATGTGTTGACATCGTTAAGGAGGCACAAAG TGCTAATCCTATGGTGATTGTAAATGCTGCTAACATACACCTGAAACATG GTGGTGGTGTAGCAGGTGCACTCAACAAGGCAACCAATGGTGCCATGCAA AAGGAGAGTGATGATTACATTAAGCTAAATGGCCCTCTTACAGTAGGAGG GTCTTGTTTGCTTTCTGGACATAATCTTGCTAAGAAGTGTCTGCATGTTG TTGGACCTAACCTAAATGCAGGTGAGGACATCCAGCTTCTTAAGGCAGCA TATGAAAATTTCAATTCACAGGACATCTTACTTGCACCATTGTTGTCAGC CGGTTCGTACACAGGTTTATATTGCAGTCAATGACAAAGCTCTTTATGAG CAGGTTGTCATGGATTATCTTGATAACCTGAAGCCTAGAGTGGAAGCACC TAAACAAGAGGAGCCACCAAACACAGAAGATTCCAAAACTGAGGAGAAAT CTGTCGTACAGAAGCCTGTCGATGTGAAGCCAAAAATTAAGGCCTGCATT GATGAGGTTACCACAACACTGGAAGAAACTAAGTTTCTTACCAATAAGTT ACTCTTGTTTGCTGATATCAATGGTAAGCTTTACCATGATTCTCAGAACA TGCTTAGAGGTGAAGATATGTCTTTCCTTGAGAAGGATGCACCTTACATG GTAGGTGATGTTATCACTAGTGGTGATATCACTTGTGTTGTAATACCCTC CAAAAAGGCTGGTGGCACTACTGAGATGCTCTCAAGAGCTTTGAAGAAAG TGCCAGTTGATGAGTATATAACCACGTACCCTGGACAAGGATGTGCTGGT TATACACTTGAGGAAGCTAAGACTGCTCTTAAGAAATGCAAATCTGCATT TTATGTACTACCTTCAGAAGCACCTAATGCTAAGGAAGAGATTCTAGGAA CTGTATCCTGGAATTTGAGAGAAATGCTTGCTCATGCTGAAGAGACAAGA AAATTAATGCCTATATGCATGGATGTTAGAGCCATAATGGCAACCATCCA ACGTAAGTATAAAGGAATTAAAATTCAAGAGGGCATCGTTGACTATGGTG TCCGATTCTTCTTTTATACTAGTAAAGAGCCTGTAGCTTCTATTATTACG AAGCTGAACTCTCTAAATGAGCCGCTTGTCACAATGCCAATTGGTTATGT GACACATGGTTTTAATCTTGAAGAGGCTGCGCGCTGTATGCGTTCTCTTA **AAGCTCCTGCCGTAGTGTCAGTATCATCACCAGATGCTGTTACTACATAT AATGGATACCTCACTTCGTCATCAAAGACATCTGAGGAGCACTTTGTAGA** AACAGTTTCTTTGGCTGGCTCTTACAGAGATTGGTCCTATTCAGGACAGC GTACAGAGTTAGGTGTTGAATTTCTTAAGCGTGGTGACAAAATTGTGTAC CACACTCTGGAGAGCCCCGTCGAGTTTCATCTTGACGGTGAGGTTCTTTC ACTTGACAAACTAAAGAGTCTCTTATCCCTGCGGGAGGTTAAGACTATAA ATGTCTATGACATATGGACAGCAGTTTGGTCCAACATACTTGGATGGTGC TGATGTTACAAAAATTAAACCTCATGTAAATCATGAGGGTAAGACTTTCT TTGTACTACCTAGTGATGACACACTACGTAGTGAAGCTTTCGAGTACTAC CATACTCTTGATGAGAGTTTTCTTGGTAGGTACATGTCTGCTTTAAACCA CACAAAGAAATGGAAATTTCCTCAAGTTGGTGGTTTAACTTCAATTAAAT GGGCTGATAACAATTGTTATTTGTCTAGTGTTTTATTAGCACTTCAACAG CTTGAAGTCAAATTCAATGCACCAGCACTTCAAGAGGCTTATTATAGAGC CCGTGCTGGTGATGCTGCTAACTTTTGTGCACTCATACTCGCTTACAGTA ATAAAACTGTTGGCGAGCTTGGTGATGTCAGAGAAACTATGACCCATCTT CTACAGCATGCTAATTTGGAATCTGCAAAGCGAGTTCTTAATGTGGTGTG TAAACATTGTGGTCAGAAAACTACTACCTTAACGGGTGTAGAAGCTG**TGA** TGTATATGGGTACTCTATCTTATGATAATCTTAAGACAGGTGTTTCCATT CCATGTGTGTGTGGTCGTGATGCTACACAATATCTAGTACAACAAGAGTC TTCTTTTGTTATGATGTCTGCACCACCTGCTGAGTATAAATTACAGCAAG GTACATTCTTATGTGCGAATGAGTACACTGGTAACTATCAGTGTGGTCAT PCT/CA2004/000626

TACACTCATATAACTGCTAAGGAGACCCTCTATCGTATTGACGGAGCTCA CCTTACAAAGATGTCAGAGTACAAAGGACCAGTGACTGATGTTTTCTACA AGGAAACATCTTACACTACAACCATCAAGCCTGTGTCGTATAAACTCGAT GGAGTTACTTACACAGAGATTGAACCAAAATTGGATGGGTATTATAAAAA GGATAATGCTTACTATACAGAGCAGCCTATAGACCTTGTACCAACTCAAC CATTACCAAATGCGAGTTTTGATAATTTCAAACTCACATGTTCTAACACA AAATTTGCTGATGATTTAAATCAAATGACAGGCTTCACAAAGCCAGCTTC ACGAGAGCTATCTGTCACATTCTTCCCAGACTTGAATGGCGATGTAGTGG CTATTGACTATAGACACTATTCAGCGAGTTTCAAGAAAGGTGCTAAATTA CTGCATAAGCCAATTGTTTGGCACATTAACCAGGCTACAACCAAGACAAC GTTCAAACCAAACACTTGGTGTTTACGTTGTCTTTGGAGTACAAAGCCAG TAGATACTTCAAATTCATTTGAAGTTCTGGCAGTAGAAGACACACAAGGA ATGGACAATCTTGCTTGTGAAAGTCAACAACCCACCTCTGAAGAAGTAGT GGAAAATCCTACCATACAGAAGGAAGTCATAGAGTGTGACGTGAAAAACTA CCGAAGTTGTAGGCAATGTCATACTTAAACCATCAGATGAAGGTGTTAAA GTAACACAAGAGTTAGGTCATGAGGATCTTATGGCTGCTTATGTGGAAAA CACAAGCATTACCATTAAGAAACCTAATGAGCTTTCACTAGCCTTAGGTT TAAAAACAATTGCCACTCATGGTATTGCTGCAATTAATAGTGTTCCTTGG AGTAAAATTTTGGCTTATGTCAAACCATTCTTAGGACAAGCAGCAATTAC AACATCAAATTGCGCTAAGAGATTAGCACAACGTGTGTTTAACAATTATA TGCCTTATGTGTTTACATTATTGTTCCAATTGTGTACTTTACTAAAAGT ACCAATTCTAGAATTAGAGCTTCACTACCTACAACTATTGCTAAAAAATAG AGTCACCCAAATTTTCTAAATTGTTCACAATCGCTATGTGGCTATTGTTG TTAAGTATTTGCTTAGGTTCTCTAATCTGTGTAACTGCTGCTTTTGGTGT ACTCTTATCTAATTTTGGTGCTCCTTCTTATTGTAATGGCGTTAGAGAAT TGTATCTTAATTCGTCTAACGTTACTACTATGGATTTCTGTGAAGGTTCT TTTCCTTGCAGCATTTGTTTAAGTGGATTAGACTCCCTTGATTCTTATCC AGCTCTTGAAACCATTCAGGTGACGATTTCATCGTACAAGCTAGACTTGA CAATTTTAGGTCTGGCCGCTGAGTGGGTTTTGGCATATATGTTGTTCACA AAATTCTTTTATTTATTAGGTCTTTCAGCTATAATGCAGGTGTTCTTTGG CTATTTTGCTAGTCATTTCATCAGCAATTCTTGGCTCATGTGGTTTATCA TTAGTATTGTACAAATGGCACCCGTTTCTGCAATGGTTAGGATGTACATC TTCTTTGCTTCTTCTACTACATATGGAAGAGCTATGTTCATATCATGGA TGGTTGCACCTCTTCGACTTGCATGATGTGCTATAAGCGCAATCGTGCCA CACGCGTTGAGTGTACAACTATTGTTAATGGCATGAAGAGATCTTTCTAT GTCTATGCAAATGGAGGCCGTGGCTTCTGCAAGACTCACAATTGGAATTG TTGCTCGTGATTTGTCACTCCAGTTTAAAAGACCAATCAACCCTACTGAC CAGTCATCGTATATTGTTGATAGTGTTGCTGTGAAAAATGGCGCGCTTCA CCTCTACTTTGACAAGGCTGGTCAAAAGACCTATGAGAGACATCCGCTCT CCCATTTTGTCAATTTAGACAATTTGAGAGCTAACAACACTAAAGGTTCA CTGCCTATTAATGTCATAGTTTTTGATGGCAAGTCCAAATGCGACGAGTC TGCTTCTAAGTCTGCTTCTGTGTACTACAGTCAGCTGATGTGCCAACCTA TTCTGTTGCTTGACCAAGCTCTTGTATCAGACGTTGGAGATAGTACTGAA GTTTCCGTTAAGATGTTTGATGCTTATGTCGACACCTTTTCAGCAACTTT TAGTGTTCCTATGGAAAAACTTAAGGCACTTGTTGCTACAGCTCACAGCG AGTTAGCAAAGGGTGTAGCTTTAGATGGTGTCCTTTCTACATTCGTGTCA GCTGCCCGACAAGGTGTTGTTGATACCGATGTTGACACAAAGGATGTTAT TGAATGTCTCAAACTTTCACATCACTCTGACTTAGAAGTGACAGGTGACA GTTGTAACAATTTCATGCTCACCTATAATAAGGTTGAAAACATGACGCCC AGAGATCTTGGCGCATGTATTGACTGTAATGCAAGGCATATCAATGCCCA AGTAGCAAAAAGTCACAATGTTTCACTCATCTGGAATGTAAAAGACTACA TGTCTTTATCTGAACAGCTGCGTAAACAAATTCGTAGTGCTGCCAAGAAG AACAACATACCTTTTAGACTAACTTGTGCTACAACTAGACAGGTTGTCAA TGTCATAACTACTAAAATCTCACTCAAGGGTGGTAAGATTGTTAGTACTT

GTTTTAAACTTATGCTTAAGGCCACATTATTGTGCGTTCTTGCTGCATTG

PCT/CA2004/000626

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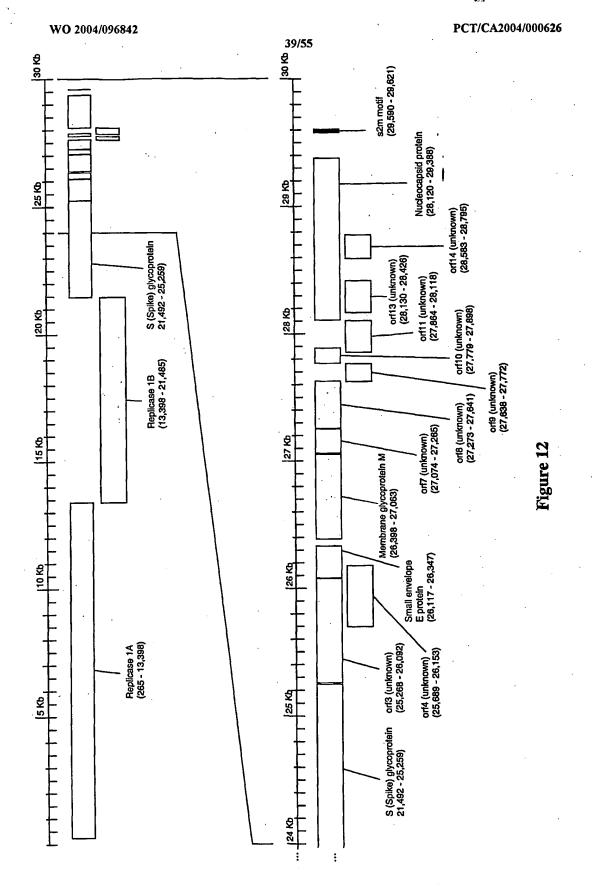
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GCTTTGTTGGAAGTGCAAATCCAAGAACCCATTACTTTATGATGCCAACT ACTTTGTTTGCTGGCACACACATAACTATGACTACTGTATACCATATAAC AGTGTCACAGATACAATTGTCGTTACTGAAGGTGACGGCATTTCAACACC AAAACTCAAAGAAGACTACCAAATTGGTGGTTATTCTGAGGATAGGCACT CAGGTGTTAAAGACTATGTCGTTGTACATGGCTATTTCACCGAAGTTTAC TACCAGCTTGAGTCTACACAAATTACTACAGACACTGGTATTGAAAATGC TACATTCTTCATCTTTAACAAGCTTGTTAAAGACCCACCGAATGTGCAAA TACACACAATCGACGGCTCTTCAGGAGTTGCTAATCCAGCAATGGATCCA ATTTATGATGAGCCGACGACGACTACTAGCGTGCCTTTGTAAGCACAAGA AAGTGAGTACGAACTTATGTACTCATTCGTTTCGGAAGAAACAGGTACGT GTCACACTAGCCATCCTTACTGCGCTTCGATTGTGTGCGTACTGCTGCAA TATTGTTAACGTGAGTTTAGTAAAACCAACGGTTTACGTCTACTCGCGTG TTAAAAATCTGAACTCTTCTGAAGGAGTTCCTGATCTTCTGGTCTAAACG AACTAACTATTATTATTATTCTGTTTGGAACTTTAACATTGCTTATCATG GCAGACAACGGTACTATTACCGTTGAGGAGCTTAAACAACTCCTGGAACA ATGGAACCTAGTAATAGGTTTCCTATTCCTAGCCTGGATTATGTTACTAC AATTTGCCTATTCTAATCGGAACAGGTTTTTGTACATAATAAAGCTTGTT TGTCTACAGAATTAATTGGGTGACTGGCGGGATTGCGATTGCAATGGCTT TCTCAATGTGCCTCTCCGGGGGACAATTGTGACCAGACCGCTCATGGAAA GTGAACTTGTCATTGGTGCTGTGATCATTCGTGGTCACTTGCGAATGGCC GGACACTCCCTAGGGCGCTGTGACATTAAGGACCTGCCAAAAGAGATCAC TGTGGCTACATCACGAACGCTTTCTTATTACAAATTAGGAGCGTCGCAGC GTGTAGGCACTGATTCAGGTTTTGCTGCATACAACCGCTACCGTATTGGA AACTATAAATTAAATACAGACCACGCCGGTAGCAACGACAATATTGCTTT GCTAGTACAGTAAGTGACAACAGATGTTTCATCTTGTTGACTTCCAGGTT ACAATAGCAGAGATATTGATTATCATTATGAGGACTTTCAGGATTGCTAT TTGGAATCTTGACGTTATAATAAGTTCAATAGTGAGACAATTATTTAAGC CTCTAACTAAGAAGAATTATTCGGAGTTAGATGATGAAGAACCTATGGAG TTAGATTATCCATAAAACGAACATGAAAATTATTCTCTTCCTGACATTGA TTGTATTTACATCTTGCGAGCTATATCACTATCAGGAGTGTGTTAGAGGT ACGACTGTACTAAAAGAACCTTGCCCATCAGGAACATACGAGGGCAA TTCACCATTTCACCCTCTTGCTGACAATAAATTTGCACTAACTTGCACTA GCACACACTTTGCTTTTGCTTGTGCTGACGGTACTCGACATACCTATCAG CTGCGTGCAAGATCAGTTTCACCAAAACTTTTCATCAGACAAGAGGAGGT TCAACAAGAGCTCTACTCGCCACTTTTTCTCATTGTTGCTGCTCTAGTAT CTTTAATTGACTTCTATTTGTGCTTTTTAGCCTTTCTGCTATTCCTTGTT TTAATAATGCTTATTATATTTTGGTTTTCACTCGAAATCCAGGATCTAGA AGAACCTTGTACCAAAGTCTAAACGAACATGAAACTTCTCATTGTTTTGA CTTGTATTTCTCTATGCAGTTGCATATGCACTGTAGTACAGCGCTGTGCA TCTAATAAACCTCATGTGCTTGAAGATCCTTGTAAGGTACAACACTAGGG GTAATACTTATAGCACTGCTTGGCTTTGTGCTCTAGGAAAGGTTTTACCT TTTCATAGATGGCACACTATGGTTCAAACATGCACACCTAATGTTACTAT CAACTGTCAAGATCCAGCTGGTGGTGCGCTTATAGCTAGGTGTTGGTACC TTCATGAAGGTCACCAAACTGCTGCATTTAGAGACGTACTTGTTGTTTTA **AATAAACGAACAAATTAAAATGTCTGATAATGGACCCCAATCAAACCAAC** GTAGTGCCCCCGCATTACATTTGGTGGACCCACAGATTCAACTGACAAT AACCAGAATGGAGGACGCAATGGGGCAAGGCCAAAACAGCGCCGACCCCA GCAAGGAGGAACTTAGATTCCCTCGAGGCCAGGGCGTTCCAATCAACACC AATAGTGGTCCAGATGACCAAATTGGCTACTACCGAAGAGCTACCCGACG  ${\tt AGTTCGTGGTGACGGCAAAATGAAAGAGCTCAGCCCCAGATGGTACT}$ TCTATTACCTAGGAACTGGCCCAGAAGCTTCACTTCCCTACGGCGCTAAC

AAAGAAGGCATCGTATGGGTTGCAACTGAGGGAGCCTTGAATACACCCAA AGACCACATTGGCACCCGCAATCCTAATAACAATGCTGCCACCGTGCTAC AACTTCCTCAAGGAACAACATTGCCAAAAGGCTTCTACGCAGAGGGAAGC AGAGGCGGCAGTCAAGCCTCTTCTCGCTCCTCATCACGTAGTCGCGGTAA TTCAAGAAATTCAACTCCTGGCAGCAGTAGGGGAAATTCTCCTGCTCGAA TGGCTAGCGGAGGTGGTGAAACTGCCCTCGCGCTATTGCTGCTAGACAGA TTGAACCAGCTTGAGAGCAAAGTTTCTGGTAAAGGCCAACAACAACAAGG CCAAACTGTCACTAAGAAATCTGCTGCTGAGGCATCTAAAAAGCCTCGCC AAAAACGTACTGCCACAAAACAGTACAACGTCACTCAAGCATTTGGGAGA CGTGGTCCAGAACAAACCCAAGGAAATTTCGGGGACCAAGACCTAATCAG ACAAGGAACTGATTACAAACATTGGCCGCAAATTGCACAATTTGCTCCAA GTGCCTCTGCATTCTTTGGAATGTCACGCATTGGCATGGAAGTCACACCT TCGGGAACATGGCTGACTTATCATGGAGCCATTAAATTGGATGACAAAGA TCCACAATTCAAAGACAACGTCATACTGCTGAACAAGCACATTGACGCAT. ACAAAACATTCCCACCAACAGAGCCTAAAAAGGACAAAAAGAAAAAGACT GATGAAGCTCAGCCTTTGCCGCAGAGACAAAAGAAGCAGCCCACTGTGAC TCTTCTTCCTGCGGCTGACATGGATGATTTCTCCAGACAACTTCAAAATT CCATGAGTGGAGCTTCTGCTGATTCAACTCAGGCATAAACACTCATGATG ACCACACAGGCAGATGGGCTATGTAAACGTTTTCGCAATTCCGTTTACG ATACATAGTCTACTCTTGTGCAGAATGAATTCTCGTAACTAAACAGCACA, AGTAGGTTTAGTTAACTTTAATCTCACATAGCAATCTTTAATCAATGTGT AACATTAGGGAGGACTTGAAAGAGCCACCACATTTTCATCGAGGCCACGC GGAGTACGATCGAGGGTACAGTGAATAATGCTAGGGAGAGCTGCCTATAT GGAAGAGCCCTAATGTGTAAAATTAATTTTAGTAGTGCTATCCCCATGTG 

GenBank Accession No. AY274119.3, SEQ ID NO: 15



# Replicase 1A

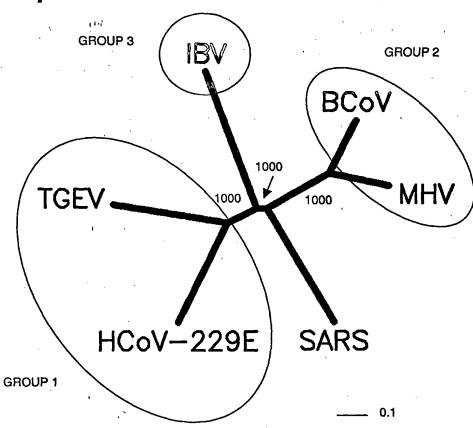


Figure 13A

# **Membrane Glycoprotein**

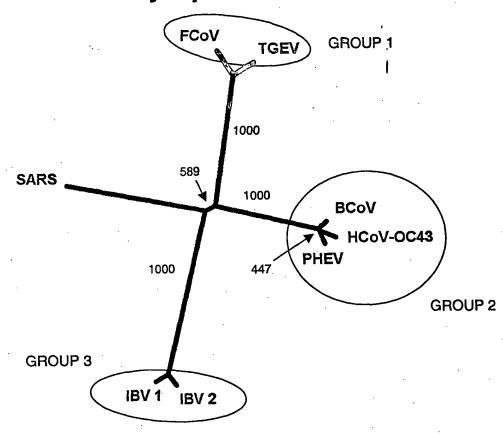


Figure 13B

# **Nucleocapsid**

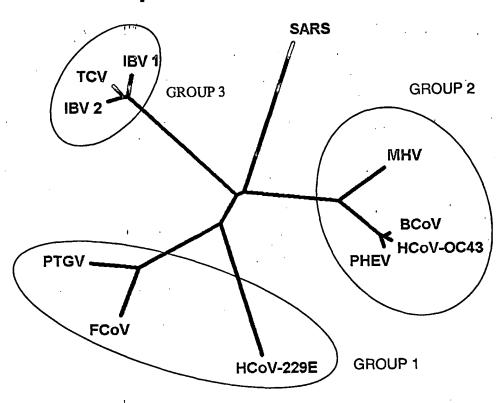


Figure 13C

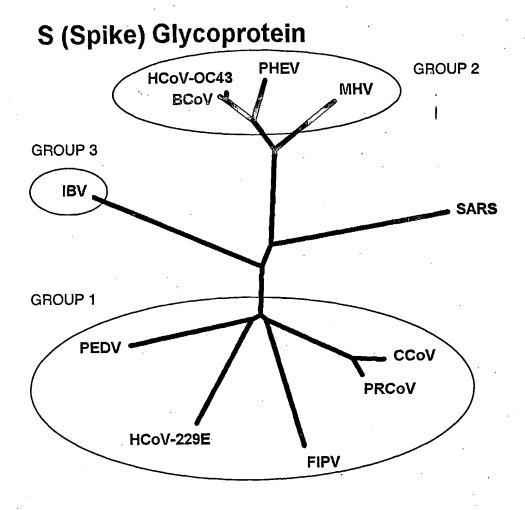


Figure 13D

229E	
PEDV	MRSLIYFWLLLPVLPTLSLPQDVTRCQSTTNFRRFFSKFNVQAPA
CCov	MIVLILCLLLFSYNSVICTSNNDCVQGNVTQLPGNENIIKDFLFHTFKEEP
PRC	
FICV	MIFIILTLLSVAKSEDAPHGVTLPOFNTSHNNERFELNFYNFLQTWDIPPNT
BoCov	MFLILLISLPMA
	MFLILLISLPMA
OC43	
PHEV	MFFILLISLPSA
MHV	MLFVFILLLPSC
TOR2_S	
AIBV	
11224	
229B	
PEDV	VVVLGGYLPSMNSSSWYCGTGIETASGVHGIFLSYIDSGQGFE
CCov	SVVVGGYYPTEVWYNCSRSATTTAYKDFSNIHAFYFDMEAMENSTG
PRC	
FICV	ETILGGYLPYCGAGVNCGWYNFSQSVGONGKYAYINTQNLNIPNVHGVYFDVREHNNDGE
BoCov	FAVIGDLKCTTVSINDVDTGAPSISTDIVDVTNGLG
OC43	LAVIGDLKCTTVAINDVDTGVPSTSTDIVDVTNGLG
	FAVIGDLKCTTSLINDVDTGVPSISSEVVDVTNGLG
PHEV	
MHV	LGYIGDFRCIQTVNYNGNNASAPSISTEAVDVSKGRG
TOR2_S	
AIBV	
	•
	<i>,</i> · ·
229B	
	IGISQEPFDPSGYQLYLHKATNGNTNATARLRICQFPDNKTLGPTVNDVTTG-
PEDV	
CCov	NARGKPLLVHVHGDPVSIIIYISAYRDDVQPRPLLKHGLLCITKNKIIDYNTFTSAQWS-
PRC	
FICV	WDDRDKVGLLIAIHGNSKYSLLMVLQDAVEANQPHVAVKICHWKPGNISSYHAFSVNLGD
BoCov	TYYVLDRVYLNTTLLLNGYYPTSGSTYRNMALKGTLLLSRLWFKPPFLSDFING-
OC43	TYYVLDRVYLNTTLLLNGYYPTSGSTYRNMALKGTLLLSRLWFKPPFLSDFING-
PHEV	TFYVLDRVYLNTTLLLNGYYPISGATFRNMALKGTRLLSTLWFKPPFLSPFNDG-
MHV	TYYVLDRVYLNATLLLTGYYPVDGSNYRNLALTGTNTLSLTWFKPPFLSEFNDG-
TOR2_S	HTSSMRGVYYPDEIFRSDTLYLTQDLFLPFYSNVTGFHTINHTFGNPVIPFKDG-
AIBV	
•	
	·
229E	
PEDV	-RNCLFNKAIPAYMRDGKDIVVGITWDNDRVT-VFADKIYHFYLKNDWSR
CCov	-AICLGDDRKIPFSVIPTDNGTKIFGLEWNDDYVTAYISDRSHHLNINNWFNNVTILYS
•	-AICHODHAIII 5411 IOAGIAII GBBAADDI 41A1 IOAGIAIGHAIAAAN 1864 1201
PRC	•
FICV	GGQCVFNQRFSLDTVLTTNDFYGFQWTDTYVDIYLGGTITKVWVDNDWSIVEAS
BoCov	IFAKVKNTKVIKKGVMYSEFPAITIGSTFVNTSYSVVVQPHTTN
OC43	IFAKVKNTKVIKHGVMYSEFPAITIGSTFVNTSYSVVVQPHTTN
PHEV	IFAKVKNSRFSKDGVIYSEFPAITIGSTFVNTSYSIVVEPHTSL
MHV	IFAKVQNLKTNTPTGATSYFPTIVIGSLFGNTSYTVVLEPYNN
TOR2_S	IYFAATEKSNVVRGWVFGSTMNNKSQSVIIINNSTNVVIRACNFELCDN
AIBV	MLGKSLFLVTILCALCSANLFDPANYVYYYQSAFRP
229E	MPVLLVAYALLHIAGCQTTNGLNTSYSVCNGCVGYSENVFAVES
PEDV	VATRCYNRRSCAMQYVYTPTYYMLNVTSAGEDG-IYYEPCTANCTGYAANVFATDS
CCov	RSSSATWQKSAAYVYQGVSNFTYYKLNNTNGLKSYELCEDYEYCTGYATNVFAPTV
PRC	MKKLFVVLVVMPLIYGDKFPTSVVSNCTDQCASYVANVFTTQP
FICV	-ISYHWNRINYGYYMQFVNRTTYYAYNNTGGANYTQLQLSECHTD-YCAGYAKNVFVP-I
BoCov	-LDNKLQGLLEISVCQYTMCEYPHTICHPKL-GNKRVELWHWDTGVVSCLYKRNFTYDVN
oc43	-LDNKLQGLLEISVCQYTMCEYPNTICHPNL-GNRRVELWHWDTGVVSCLYKRNFTYDVN
PHEV	-INGNLQGLLQISVCQYTMCEYPHTICHPNL-GNQRIELWHYDTDVVSCLYRRNFTYDVN
MHV	IIMASVCTYTICQLPYTPCKPNTNGNRVIGFWHTDVKPPICLLKRNFTFNVN
TOR2_S	PFFAVSKPMGTQTHTMIFDNAFNCTFEYISDAFSLDVSEKSGNFKHLREFVFKNKDG
AIBV	SNGWHLOGGAYAVVNSSNYANNAGSASECTVGVIKDVYNQSAASIAMTAPLQG
WYDA	AGATUDAGODTUA AMODINTENINGODGECTAGATUDA IMÃOUUQTUITUE DÃO

45/55

229E	GGYIPSDFAFNNWFLLTNTSSVVDGVVRSFQPLLLNCLWSVSGLRFTTGFVYFNGTGR
PEDV	NGHIPEGFSFNNWFLLSNDSTLLHGKVVSNQPLLVNCLLAIPKIYGLGQFFSFNHTMD
CCov	GGYIPHGFSFNNWFMRTNSSTFVSGRFVTNQPLLVNCLWPVPSFGVAAQQFCFEGAQF
PRC	GGFIPSDFSFNNWFLLTNSSTLVSGKLVTKQPLLVNCLWPVPSFEEAASTFCFEGADF
FICV	DGKIPEDFSFSNWFLLSDKSTLVQGRVLSSQPVFVQCLRPVPSWSNNTAVVHFKN-D
BoCov	ADYLYFHFYQEGGTFYAYFTDTGVVTKFLFNVYLGTVLSHYYVLPLTCSSAMTLEY
OC43	ADYLYFHFYQEGGIFYAYFTDTGVVTKFLFNVYLGTVLSYYYVMPLTCNSAMTLEY
PHEV	ADYLYFHFYQEGGTFYAYFTDTGFVTKFLFKLYLGTVLSHYYVMPLTCNSALSLEY
MHV	APWLYFHFYQQGGTFYAYYADKPSATTFLFSVYIGDILTQYFVLPFICTPTAGSTLAPLY
TOR2_S	FLYVYKGYQPIDVVRDLPSGFNTLKPIFKLPLGINITNFRAILTAFSPAQDIWGTSAAAY
AIBV	MAWSKSQFCSAHCDFSEITVFVTHCYSSGSGSCPITGMIARGHIRISAMKNGSLFVNLTV
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	· ·
229E	GDCKGFSSDVLSDVIRYNLN-FEENLRRGTILFKTSYGV-VVFYCTNNT
PEDV	GVCNGAAVDRAPEALRFNINDTSVILAEGSIVLHTALGTNLSFVCSNSSD
CCov	SQCNGVSLNNTVDVIRFNLN-FTALVQSGMGATV-FSLNTTGGVILEISCYNDTVSB
PRC	DQCNGAVLNNTVDVIRFNLN-FTTNVQSGKGATV-FSLNTTGGVTLEISCYNDTVSD
FICV	AFCPNVTADVLRFNLNFSDTDVYTDSTNDEQLFFTFEDNTTASIACYSSANVTDFQ
BoCov	WVTPLTSKQYLLAFNQDGVIFNAVDCKSDFMSEIKCKTLSIAPSTGVYELNG
OC43	WVTPLTSKQYLLAFNQDGVIFNAVDCKSDFMSEIKCKTLSIAPSTGVYELNG
PHEV	WVTPLTTRQFLLAFDQDGVLYHAVDCASDFMSEIMCKTSSITPPTGVYELNG
MHV	WVTPLLKRQYLFNFNEKGVITSAVDCASSYISEIKCKTQSLLPSTGVYDLSG
TOR2_S	FVGYLKPTTFMLKYDENGTITDAVDCSQNPLAELKCSVKSFEIDKGIYQTSN
AIBV	SVSKYPNFKSFQCVNNFTSVYLNGDLVFTSNKTTDVTSAGVYFKAGGPVNYSIMK
	•
229E	-LVSGDAHIPFGTVLGNFYCFVNTTIGTETTSAFVGALPKTVREFVISRTGHFYINGYRY
PEDV	-PHLAIFAIPLGATEVPYYCFLKVDTYNSTVYKFLAVLPSTVREIVITKYGDVYVNGFGY
CCov .	SSFYSYGEISFGVTDGPRYCFALYNGTALKYLGTLPPSVKEIAISKWGHFYINGYNF
PRC	SSFSSYGEIPFGVTNGPRYCYVLYNGTALKYLGTLPPSVKEIAISKWGHFYINGYNF
FICV	PANNSVSHIPFGKTAHFCFAN-FSHSIVSRQFLGILPPTVREFAFGRDGSIFVNGYKY
BoCov	-YTVQPIADVYRRIPNLPDCNIEAWLNDKSVPSPLNWERKTFSNCNFNMSSLMSFIQADS
OC43	-YTVQPIADVYRRIPNLPDCNIEAWLNDKSVPSPLNWERKTFSNCNFNMSSLMSFIQADS
PHEV	-YTVQPVATVYRRIPDLPNCDIEAWLNSKTVSSPLNWERKIFSNCNFNMGRLMSFIQADS
MHV	-YTVQPVGVVYRRVPNLPDCKIEEWLTAKSVPSPLNWERRTFQNCNFNLSSLLRYVQAES
TOR2_S	-FRVVPSGDVVRFPNITNLCPFGEVFNATKFPSVYAWERKKISNCVADYSVLYNSTFFST
AIBV	-EFKVLAYFVNGTAQDVILCDNSPKGLLACQYNTGNFSDGFYPFTNSTLVREKFIVYRES
	*
229B	FTLGNVEAVNFNVTTAETTD~~~FFTVALASYADVLVNVSQTSIANIIYCNSVINRLRC
PEDV	LHLGLLDAVTIYFTGHGTDDDVSGFWTIASTNFVDALIEVQGTSIQRILYCDDPVSQLKC
CCov	FSTFPIDCISFNLTTGDSGAFWTIAYTSYTDALVQVENTAIKKVTYCNSHINNIKC
PRC	FSTFPIDCISFNLTTGDSDVFWTIAYTSYTEALVQVENTAITNVTYCNSYVNNIKC
FICV	FSLPAIRSVNFSISSVEEYGFWTIAYTNYTDVMVDVNGTAITRLFYCDSPLNRIKC
BoCov	FTCNNIDAAKIYGMCFSSITIDKFAIPNGRKVDLQLGNLGYLQSFNYRIDTTATSC
OC43	FTCNNIDAAKIYGMCFSSITIDKFAIPNGRKVDLQLGNLGYLQSFNYRIDTTATSC
PHEV	FGCNNIDASRLYGMCFGSITIDKFAIPNSRKVDLQVGKSGYLQSFNYKIDTAVSSC
MHV	LSCNNIDASKVYGMCFGSVSVDKFAIPRSRQIDLQIGNSGFLQTANYKIDTAATSC
TOR2_S	FKCYGVSATKLNDLCFSNVYADSFVVKGDDVRQIAPGQTGVIADYNYKLPDDFMGC
AIBV	SVNTTLALTNFTFTNVSNAQPNSGGVHTFHLYQTQTAQSGYYNFNLSFLSQFVYKA
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PEDV	SQVAFDLDDGFYPISSRNLLSHEQPISFVTLPSFNDHSFVNITVSAA
CCov	SQLTANLQNGFYPVASSEVGLVNKSVVLLPSFYSHTSVNITIDLGMKR
PRC	SQLTANLNNGFYPVSSSEVGSVNKSVVLLPSFLTHTIVNITIGLGMKR
FICV	QQLKHELPDGFYSASMLVKKDLPKTFVTMPQFYHWMNVTLHVVLNDTEKK
BoCov	-QLYYNLPAANVSVSRFNPSTWNRRFGFTEQFVFKPQPVGVFTHHDVVYAQHCFKAPKNF
OC43	-QLYYNLPAANVSVSRFNPSIWNRRFGFTEQSVFKPQPAGVFTDHDVVYAQHCFKAPTNF
PHEV	-QLYYSLPAANVSVTHYNPSSWNRRYGFNNQSFGSRGLHDAVYSQQCFNTPNTY
MHV	-QLYYSLPKNNVTINNYNPSSWNRRYGFKVND
TOR2_S	-VLAWNTRNIDATSTGNYNYKYRYLRHG
AIBV	SDYMYGSYHPICAFRPETINSGLWFNSLS

229E PEDV CCOV PRC FICV	SGGGKCFNCYPAGVNITLANFNETKGPLCVDTSHFTTKYVAVYANFGGLSSANLVASDTTINGFSSFCVDTRQFTITLFYNVTNSSGYGQPIASTLSNITLPMQDNNTDVYCIRSNRFSVYFHSTCKSSLWDDVFNSSGYGQPIASTLSNITLPMQDNNTDVYCVRSDQFSVYVHSTCKSALWDNVFKR YDIILAKAPELAALADVHFEIAQANGSVTNVTSLCVQARQLALFYKYTSL
BoCov OC43	CPCKLDGSLCVGNGPGIDAGYKNSGIGTCPAGTNYLTCHNAAQCDCCPCKLDGSLCVGNGPGIDAGYKNSGIGTCPAGTNYLTCHNAVQCNC
PHEV MHV	CPCRTSQCIGGAGTGTCPVGTTVRKCPAAVTKATKCTC
TOR2_S AIBV	
	vgrwsasintgncpfsfgkvnnfvkfgsvcfslkdipgg-campivanwayskyyt
229E PEDV CCov	YGYVSKSQDS-NCPFTLQSVNDYLSFSKFCVSTSLLAGA-CTIDLFGYPAFGSGVK DCTDVLYATAVIKTGTCPFSFDKLNNYLTFNKFCLSLNPVGAN-CKFDVAARTRTNEQVV
PRC FICV BoCov	NCTDVLDATAVIKTGTCPFSFDKLNNYLTFNKFCLSLSPVGAN-CKFDVAARTRTNEQVV QGLYTYSNLVELQNYDCPFSPQQFNNYLQFETLCFDVNPAVAG-CKWSLVHDVQWRTQFA LCTPDPITSKSTGPYKCPQTKYLVGIGEHCSGLAIKSDYCGGNPCTCQPQAFLGWSVDSC
OC43 PHEV	LCTPDPITSKSTGPYKCPQTKYLVGIGEHCSGLAIKSDYCGGNPCTCQPQAFLGWSVDSC WCQPDPSTYKGVNAWTCPQSKVSIQPGQHCPGLGLVEDDCSGNPCTCKPQAFIGWSSETC
MHV TOR2_S AIBV	KLRPFERDISNVPFSPDGKPCTPPALN-CYWPLNDYGFYTTTGI
229E PEDV CCov	IG+TLYVSWSDGDGITGVPQ-PVEGVSSFMNVTLDKCTKYNIYDVSGVGVIRVSNDT LTSLYFQFTKGELITGTPK-PLEGITDVSFMTLDVCTKYTIYGFKGEGIITLTNSS RSLYVIYEEGDNIVGVPS-DNSGLHDLSVLHLDSCTDYNIYGITGVGIIRQTNST
PRC FICV	RSLYVIYEEGDSIVGVPS-DNSGLHDLSVLHLDSCTDYNIYGRTGVGIIRQTNRT TITVSYKHGSMITTHAKGHSWGFQDTSVLVKDECTDYNIYGFQGTGIIRNTTSR
BoCov OC43	LQGDRCNIFANFIFHDVNSGTTC-STDLQKSNTDIILGVCVNYDLYGITGQGIFVEVNAT LQGDRCNIFANFILHDVNSGTTC-STDLQKSNTDIILGVCVNYDLYGITGQGIFVEVNAP
PHEV MHV	LQNGRCNIFANFILNDVNSGTTC-STDLQQGNTIITTDVCVNYDLYGITGQGILIEVNAT RCQIFANILLNGINSGTTC-STDLQLPNTEVATGVCVRYDLYGITGQGVFKEVKAD
TOR2_S AIBV	GYQPYRVVVLSFELLNAPA-TVCGPKLSTDLIKNQCVNFNFNGLTGTGVLTPSSKR LLVYVTKSDGSRIQTRTEPLVLTQHNYNNITLDKCVAYNIYGRVGQGFITNVTDS : . * . : . * * . :
229E	FLNGITYTSTSGNLLGFKDVTKGTIYSITPCNPPDQLVVYQQAVVGAM
PEDV CCov	ILAGVYYTSDSGQLLAFKNVTSGAVYSVTPCSFSEQAAYVNDDIVGVI LLSGLYYTSLSGDLLGFKNVSDGVIYSVTPCDVSAHAAVIDGAIVGAM
PRC FICV	LLSGLYYTSLSGDLLGFKNVSDGVIYSVTPCDVSAQAAVIDGTIVGAI LVAGLYYTSISGDLLAFKNSTTGEIFTVVPCDLTAQVAVINDEIVGAI
BoCov OC43	YYNSWONLLYDSNGNLYGFRDYLTNRTFMIRSCYSGRVSAAFHANSSEPAL YYNSWONLLYDSNGNLYGFRDYLTNRTFMIRSCYSGRVSAAFHANSSEPAL
PHEV MHV	YYNSWQNLLYDSSGNLYGFRDYLSNRTFLIRSCYSGRVSAVFHANSSEPAL YYNSWQALLYDVNGNLNGFRDLTTNKTYTIRSCYSGRVSAAYHKEAPEPAL
TOR2_S AIBV	FQPFQQFGRDVSDFTDSVRDPKTSEILDISPCAFGGVSVITPGTNASSEVAV VANFSYLADGGLAILDTSGAIDVFVVQGSYGLNYYKVNPCEDVNQQFVVSGGNIVGIL
229E PEDV	LSENFTSY
CCov PRC	TSINSELLGLTHWTTTPNFYYYSIYNYTNERTRGTAIDSND TSINSELLGLTHWTITPNFYYYSIYNYTNDKTRGTPIDSND
FICV BoCov	TAVNQTDLFEFVNNTQARRSRSSTPNFVTSYTMPQFYYITKWNNDTS-SLFRNIKCNYVFNNTLSRQLQPINYFDSYLGCVVNADNSTS
OC43 PHEV	LFRNIKCNYVFNNTLSRQLQPINYFDSYLGCVVNADNSTA MFRNLKCSHVFNNTILRQIQLVNYFDSYLGCVVNAYNNTA
MHV	LYRNINCSYVFTNNISREENPLNYFDSYLGCVVNADNRTD
TOR2_S AIBV	LYQDVNCTDVSTAIHADQLTPAWRIYSTGNNVFQTQAGCLIGAEHV TSRNETGS
229E	-CTDAVLTYSSFGVCADGSIIAVQPRNVSYDSVSAIVTANLS
PEDV CCov	-CTEPVLVYSNIGVCKSGSIGYVPSQYGQVKIAPTVTGNISVDCEPIITYSNIGVCKNGALVFINVTHSDGDVQPISTGNVT
PRC FICV	VGCEPVITYSNIGVCKNGALVFINVTHSDGDVQPISTGNVT
BoCov	SVVQTCDLTVGSGYCVDYSTKRRSR-RAITTGYRFTNFEPFTVNSVNDSLEPVGGLYEIQ

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OC43 PHEV MHV TOR2_S AIBV	SAVQTCDLTVGSGYCVDYSTKRRSR-RAITTGYRFTNFEPFTVNSVNDSLEHVGGLYEIQ SAVSTCDLTVGSGYCVDYVTALRSR-RSPTTGYRFTNFEPFAANLVNDSIEPVGGLYEIQ EALPNCNLRMGAGLCVDYSKSRRAR-RSVSTGYRLTTFEPYMPMLVNDSVQSVGGLYEMQ DTSYECDIPIGAGICASYHTVSLLRSTSQKSIVAYTMSLGADSSIAYSNNTIA QNVTSCPYVSYGRFCIEPDGSLKMIVPEELKQFVAPLLNITESVL
229E PEDV CCOV PRC FICV BOCOV OC43 PHEV MHV TOR2_S AIBV	IPSNWTISVQVEYLQITSTPIVVDCSTYVCNGNVRCVELLKQYTSACKTIEDALRNSARL IPTNFSMSIRTEYLQLYNTPVSVDCATYVCNGNSRCKQLLTQYTAACKTIESALQUSARL IPTNFTISVQVEYIQVYTTPVSIDCSRYVCNGNPRCNKLLTQYVSACQTIEQALAMGARL IPTNFTISVQVEYIQVYTTPVSIDCSRYVCNGNPRCNKLLTQYVSACQTIEQALAMGARL IPKNFTVAVQAEYIQIQVKPVVVDCATYVCNGNTHCLKLLTQYTSACQTIENALNLGARL IPSEFTIGNMEEFIQTSSPKVTIDCSAFVCGDYAACKSQLVEYGGFCDNINATLITEVNEL IPSEFTIGNMEEFIQTSSPKVTIDCSAFVCGDYAACKSQLVEYGGFCDNINATLITEVNEL IPSEFTIGNLEEFIQTRSPKVTIDCATFVCGDYAACRQQLAEYGSFCENINAILTEVNEL IPTNFTIGHHEEFIQIRAPKVTIDCAAFVCGDNAACRQQLVEYGGFCDNVNATLNEVNNL IPTNFSISITTEVMPVSMAKTSVDCNMYICGDSTECANLLLQYGGFCTQLNRALSGIAAE IPNSFNLTVTDEYIQTRMDKVQINCLQYVCGNSLECRKLFQQYGFVCDNILSVVNSVSQK **:
229E	ESADVSEMLTFDKKAFTLANVSSF-GDYNLSSVIPSLPTSGSR
PEDV	ESVEVNSMLTISEEALQLATISSFNGDGYNFTNVLGASVYDPASGRV
CCov	ENMEIDSMLFVSENALKLASVEAFNSTETLDPIYKEWPNIGGSWLGGLKDILPSHNSK
PRC	ENMEVDSMLFVSENALKLASVEAFNSSETLDPIYTQWPNIGGFWLEGLKYILPSDNSK ESLMLNDMITVSDRGLELATVERFNATALGGEKLGGLYFDGLSSLLPPK
FICV BoCov	LDTTQLQVANSLMNGVTLSTKLKDGVNFNVDDINFSPVLGCLGSACNK
OC43	LDTTQLQVANSLMNGVTLSTKLKDGVNFNVDDVNFSPVLGCLGSECNK
PHEV	LDTTQLQVANSLMNGVTLSTKIKDGINFNVDDINFSPVLGCLGSECNR
VHM	LDNMQLQVASALMQGVTISSRLPDGISGPIDDINFSPLLGCIGSTCAEDG
TOR2_S	QDRNTREVFAQVKQMYKTPTLKYFGGFNFSQILPDPLKP
AIBV	EDMELLSFYSSTKPKGYDTPVLSNVSTGEFNISLLLTPPSSP
•	
229E	VAGRSAIEDILFSKIVTSGLGTVDADYKNCTKGLSIADLACAQYYNGIMVLPG
PEDV	VQKRSVIEDLLFNKVVTNGLGTVDEDYKRCSNGRSVADLVCAQYYSGVMVLPG
CCov	RKYRSAIEDLLFDKVVTSGLGTVDEDYKRCTGGYDIADLVCAQYYNGIMVLPG
PRC	RKYRSAIEDLLFSKVVTSGLGTVDEDYKRCTGGYDIADLVCAQYYNGIMVLPG
FICV	IGKRSAVEDLLFNKVVTSGLGTVDDDYKKCSSGTDVADLVCAQYYNGIMVLPG
BoCov	VSSRSAIEDLLFSKVKLSDVG-FVEAYNNCTGGAEIRDLICVQSYNGIKVLPP
OC43	VSSRSAIEDLLFSKVRLSDVG-FVEAYNNCTGGAGIRDLICVQSYNGIKVLPP
PHEV	ASTRSAIEDLLFDKVKLSDVG-FVQAYNNCTGGAEIRDLICVQSYNGIKVLPP. NGPSAIRGRSAIEDLLFDKVKLSDVG-FVEAYNNCTGGQEVRDLLCVQSFNGIKVLPP
MHV	NGPSATRGRSATEDLLFDKVKLSDVG-FVEATRICTGGQE-VKDDDCVQSFRGTKVDFFTKRSFTEDLLFNKVTLADAG-FMKQYGECLGDINARDLICAQKFNGLTVLPP
TOR2_S AIBV	SGRSFVEDLLFTSVETVGLP-TDAEYKKCTAGPLGTLKDLICAREYNGLLVLPP
*****	** :**:** ;
	CANCEL TO THE PROPERTY OF THE
229E	VADAERMAMYTGSLIGGIALGGLTSAVSIPFSLAIQARLNYVALQTDVLQENQKIL VVDAEKLHMYSASLIGGMALGGITAAAALPFSYAVQARLNYLALQTDVLQRNQQLL
PEDV CCov	VANDDKMAMYTASLAGGITLGSLGGGAVSIPFAIAVQARLNYVALQTDVLNKNQQIL
PRC	VANADKMTMYTASLAGGITLGAFGGGAVSIPFAVAVQARLNYVALQTDVLNKNQQIL
FICV	VVDGNKMSMYTASLIGGMALGSITSAVAVPFAMQVQARLNYVALQTDVLQENQKIL
BoCov	LLSVNQISGYTLAATSASLFPPLSAAVGVPFYLNVQYRINGIGVTMDVLSQNQKLI
OC43	LLSDNQISGYTLAATSANLFPPWSAAAGVPFYLNVQYRINGIGVTMDVLSQNQKLI
PHEV	LLSENQISGYTLAATAASLFPPWTAAAGVPFYLNVQYRINGLGVTMDVLSQNQKLI
VHM	VLSESQISGYTAGATAAAMFPPWTAAAGVPFSLNVQYRINGLGVTMNVLSENQKMI
TOR2_S	LLTDDMIAAYTAALVSGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKQI IITADMQTMYTASLVGAMAFGGITSAAAIPFATQIQARINHLGIAQSLLMKNQEKI
AIBV	: . *: .: .: *: *: : *: :: :: :: :: :: :: :: :: ::
229E	AASFNKAMTNIVDAFTGVNDAITQTSQALQTVATALNKIQDVVNQQGNSLNHLTSQLRQN
PEDV	AESFNSAIGNITSAFESVKEAISQTSKGLNTVAHALTKVQEVVNSQGSALNQLTVQLQHN
CCov	ANAFNQAIGNITQAFGKVNDAIHQTSQGLATVAKVLAKVQDVVNTQGQALSHLTLQLQNN
PRC	ASAFNQAIGNITQSFGKVNDAIHQTSRGLTTVAKALAKVQDVVNTQGQALRHLTVQLQNN
FICV	ANAFNNAIGNITLALGKVSNAITTTSDGFNSMASALTKIQSVVNQQGEALSQLTSQLQKN ANAFNNALDAIQEGFDATNS-ALVKIQAVVNANAEALNNLLQQLSNR
BoCov OC43	ANAFNNALDAIQEGFDATNS-ALVKIQAVVNADAEALNNLLQQLSNR
PHEV	ASAFNNALDAIQEGFDATNS-ALVKIQAVVNANAEALNNLLQQLSNR
MHV	ASAFNNALGAIQEGFDATNS-ALGKIQSVVNANAEALNNLLNQLSNR
TOR2_S	ANQFNKAISQIQESLTTTSTALGKLQDVVNQNAQALNTLVKQLSSN
AIBV	AASFNKAIGHMQEGFRSTSLALQQVQDVVNKQSAILTETMNSLNKN
	* **.*: : .:* .* .* .* .

```
FQAISSSIQAIYDRLDTIQADQQVDRLITGRLAALNVFVSHTLTKYTEVRASRQLAQQKV
229E
                FQAISSSIDDIYSRLDILLADVQVDRLITGRLSALNAFVAQTLTKYTEVQASRKLAQQKV
PEDV
                FQAISSSISDIYNRLDELSADAQVDRLITGRLTALNAFVSQTLTRQAEVRASRQLAKDKV
CCov
                FOAISSSISDIYNRLDELSADAQVDRLITGRLTALNAFVSQTLTRQAEVRASRQLAKDKV
PRC
                FQAISSSIAEIYNRLEKVEADAQVDRLITGRLAALNAYVSQTLTQYAEVKASRQIALEKV
FICV
                FGAISSSLQEILSRLDALEAQAQIDRLINGRLTALNVYVSQQLSDSTLVKFSAAQAMEKV
BoCov
                FGAIŞŞSLQEILSRLDALEAQAQIDRLINGRLTALDAYVSQQLSDSTLVKFSAAQAMEKV
OC43
                FGAISASLQEILSRLDALEAKAQIDRLINGRLTALNAYVSQQLSDSTLVKFSAAQAIEKV
PHEV
                FGAISASLQEILTRLDAVEAKAQIDRLINGRLTALNAYISKQLSDSTLIKFSAAQAIEKV
MHV
                FGAISSVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKM
TOR2 S
                   FGAISSVIQDIYAQLDAIQADAQVDRLITGRLSSLSVLASAKQSEYIRVSQQRELATQKI
AIBV
                          * ;*; ; *, *;****,*** ;*..
                NECVKSQSKRYGFCG-NGTHIFSIVNAAPEGLVFLHTVLLPTQYKDVEAWSGLCV-DG--
229B
PEDV
                NECVKSOSORYGFCGGDGEHIFSLVQAAPQGLLFLHTVLVPGDFVNVLAIAGLCV-NG--
CCov
                NECVRSQSQRFGFCG-NGTHLFSLANAAPNGMIFFHTVLLPTAYETVTAWSGICASDGDR
                NECVRSQSQRFGFCG-NGTHLFSLANAAPNGMIFFHTVLLPTAYETVTAWSGICALDGDR
PRC
FICV
                NECVKSQSNRYGFCG-NGTHLFSLVNSAPEGLLFFHTVLLPTEWEEVTAWSGICVNDT--
                NECVKSQSSRINFCG-NGNHIISLVQNAPYGLYFIHFSYVPTKYVTAKVSPGLCI----
BoCov
                NECVKSQSSRINFCG-NGNHIISLVQNAPYGLYFIHFSYVPTKYVTAKVSPGLCI-----
OC43
                NECVKSQSSRINFCG-NGNHIISLVQNAPYGLYFIHFSYVPTKYVTAKVSPGLCI---
PHRV
                NECVKSQTTRINFCG-NGNHILSLVQNAPYGLCFIHFSYVPTSFKTANVSPGLCI----
MHV
                SECVLGQSKRVDFCG-KGYHLMSFPQAAPHGVVFLHVTYVPSQERNFTTAPAICH----
TOR2_S
                   NECVKSQSNRYGFCG-SGRHVLSIPQNAPNGIVFIHFTYTPETFVNVTAIVGFCVNPLNA
AIBV
                     .*: * .*** .* *::*: : ** *: *:*.
229E
                TNGYVLRQPNLALYK-----EGNYYRITSRIMFEPRIPTMADFVQIENCNVTFVNISRS
                EIALTLREPGLVLFTHELQTYTATEYFVSSRRMFEPRKPTVSDFVQIESCVVTYVNLTSD
PEDV
                TFGLVVKDVQLTLFRN-----LDDKFYLTPRTMYQPIVATSSDFVQIEGCDVLFVNATVI
CCov
                TFGLVVKDVQLTLFRN----LDDKFYLTPRTMYQPRVATSSDFVQIEGCDVLFVNTTVS
PRC
                -YAYVLKDFDHSIFS----YNGTYMVTPRNMFQPRKPQMSDFVQITSCEVTFLNMTYT
FICV
                -AGDRGIAPKSGYFVN-----VNNTWMFTGSGYYYPEPITGNNVVVMSTCAVNYTKAPDV
BoCov
                -AGDRGIAPKSGYFVN-----VNNTWMFTGSRYYYPEPITGNNVVVMSTCAVNYTKAPDV
OC43
                -AGDIGISPKSGYFIN----VNNSWMFTGSSYYYPEPITQNNVVVMSTCAVNYTKAPDL
PHEV
                -SGDRGLAPKAGYFVQ----DNGEWKFTGSNYYYPEPITDKNSVAMISCAVNYTKAPEV
MHV
                -EGKAYFPREGVFVFN-----GTSWFITQRNFFSPQIITTDNTFVSGNCDVVIGIINNT
TOR2_S
                   SQYAIVPANGRGIFIQ----VNGTYYITSRDMYMPRDITAGDIVTLTSCQANYVNVNKT
AIBV
                                          : .:
                ELOTIVP-EYIDVNKTLOELSYKL-PNYTVPDLV---VEQYNQTILNLTSEISTLENKSA
229E
                QLPDVIP-DYIDVNKTLDEILASL-PNRTGPSLP---LDVFNATYLNLTGEIADLEQRSE
PEDV
                DLPSIIP-DYIDINQTVQDILENFRPNWTVPELP---LDIFNATYLNLTGEINDLEFRSE
CCov
                DLPSIIP-DYIDINQTVQDILENFRPNWTVPELT---LDVFNATYLNLTGEIDDLEFRSE
PRC
                TFQEIVI-DYIDINKTIADMLEQYNPNYTTPELNL-LLDIFNQTKLNLTAEIDQLEQRAD
FICV
                MINISTP-NLHDFKEELDQWFKNQ--TSVAPDLSL-DY--INVTFLDLQDEMN------
MLNISTP-NLPDFKEELDQWFKNQ--TLVAPDLSL-DY--INVTFLDLQDEMN------
BoCov
OC43
                MLNTSTP-NLPDFKEELYQWFKNQ--SSVAPDLSL-DY--INVTFLDLQDEMN------
PHEV
                FLNNSIP-NLPDFKEELDKWFKNQ--TSIAPDLSL-DFEKLNVTFLDLTYEMN-----
MHV
                VYDPLOP-ELDSFKEELDKYFKNH----TSPDVDLGDISGINASVVNIQKEID-----
TOR2 S
                   VITTFVEDDDFNFDDELSKWWNDT--KHGLPDFD---DFNYTVPILNISGEID------
AIBV
                            .... : .
                                                           . . :::
                ELNYTVQKLQTLIDNINSTLVDLKWLNRVETYIKWPWWVWLCISVVLIFVVSMLLLCCCS
229E
                SLRNTTEELRSLINNINNTLVDLEWLNRVETYIKWPWWVWLIIVIVLIFVVSLLVFCCIS
PEDV
                KLHNTTVELAILIDNINNTLVNLEWLNRIETYVKWPWYVWLLIGLVVIFCIPILLFCCCS
CCov
                KLHNTTVELAILIDNINNTLVNLEWLNRIETYVKWPWYVWLLIGLVVIFCIPLLLFCCCS
PRC
                NLTTIAHELQQYIDNLNKTLVDLDWLNRIETYVKWPWYVWLLIGLVVVFCIPLLLFCCLS
FICV
                     ---RLQEAIKVLNQSYINLKDIGTYEYYVKWPWYVWLLIGFAGVAMLVLLFFICCC
BoCov
                     ---RLQEAIKVLNQSYINLKDIGTYEYYVKWPWYVWLLIGFAGVAMLVLLFFICCC
OC43
                -----RLQEAIKVLNQSYINLKDIGTYEYYVKWPWYVWLLIGLAGVAMLVLLFFICCC
PHEV
                 -----RIQDAIKKLNESYINLKEVGTYEMYVKWPWYVWLLIGLAGVAVCVLLFFICCC
MHV
                    ----rlnevaknlneslidlqelgkyeqyikwpwyvwlgfiagliaivmvtillccm
TOR2_S
                       ---NIQGVIQGLNDSLINLEELSIIKTYIKWPWYVWLAIGFAIIIFILILGWVFFM
AIBV
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229E PEDV CCOV PRC FICV BoCov OC43 PHEV MHV		TGCCG-FFSCFASSIRGCCESTKL-PYYDVEKIHIQ TGCCG-CCGCCGACFSGCCRGPRLQPYEAFEKVHVQ TGCCG-CIGCLGSCCHSICSRRQFESYEPIEKVHVH TGCCG-CIGCLGSCCHSICSRRQFENYEPIEKVHVH TGFCG-CFGCVGSCCHSLCSRRQFETYEPIEKVHIH TGCGTSCFKICGGCCD-DYTCHQELVIKTSHDD TGCGTSCFKKCGGCCD-DYTCHQELVIKTSHEG TGCGTSCFKKCGGCCD-DYTCHQEFVIKTSHDD TGCGTSCFKKCGGCCD-DYTCHQEFVIKTSHDD TGCGSCCFRKCGSCCD-EYGCHQDSIVIHNISAHED						
TOR2_S AIBV	>	TSCCSCLKGACSCGSCCKFDEDDSEPVLKGVKLHYT TGCCGCCCGCFGIIPLISKCGKKSSYYTTFDNDVVTEQYRPKKSV	1					٠.
CCOV FICV MHV OC43 PEDV PHEV PRC	spike glycops spike prot peplomer ; E2 glycops surface ps surface ps spike prot spike glyc S protein	coprotein [Human coronavirus 229E]. coprotein [Avian infectious bronchitis virus]. cotein precursor (Spike glycoprotein) cein - canine coronavirus protein [Feline infectious peritonitis virus]. cotein precursor (Spike glycoprotein) cotein - human coronavirus cein [Porcine epidemic diarrhea virus]. coprotein [porcine hemagglutinating encephalomyelitis virus].	S41453 BAA06805 P11225 S44241 CAA80971	28.6% 27.6% 30.5% 26.1% 25.4% 31.9% 30.7% 26.0% 30.5%	(SEQ (SEQ (SEQ (SEQ (SEQ (SEQ (SEQ	ID N ID N ID N ID N ID N	0: 0: 0: 0: 0: 0:	54) 55) 56) 57) 58) 59) 60) 61)

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10 20 TOR2\_E PGV 50 20 30 40 10 70 60 TOR2\_E YVYSRVKNLNSSEGVPDLLV (SEQ ID NO: 35) HAYDAYKNFMRIKAYNPDGALLA (SEQ ID NO: 63) 80 70

FIGURE 15

MESLVLGVNEKTHVQLSLPVLQVRDVLVRGFGDSVEEALSEAREHLKNGT CGLVELEKGVLPQLEQPYVFIKRSDALSTNHGHKVVELVAEMDGIQYGRS GITLGVLVPHVGETPIAYRNVLLRKNGNKGAGGHSYGIDLKSYDLGDELG TDPIEDYEQNWNTKHGSGALRELTRELNGGAVTRYVDNNFCGPDGYPLDC IKDFLARAGKSMCTLSEQLDYIESKRGVYCCRDHEHEIAWFTERSDKSYE HQTPFEIKSAKKFDTFKGECPKFVFPLNSKVKVIQPRVEKKKTEGFMGRI RSVYPVASPQECNNMHLSTLMKCNHCDEVSWQTCDFLKATCEHCGTENLV IEGPTTCGYLPTNAVVKMPCPACQDPEIGPEHSVADYHNHSNIETRLRKG GRTRCFGGCVFAYVGCYNKRAYWVPRASADIGSGHTGITGDNVETLNEDL LEILSRERVNINIVGDFHLNEEVAIILASFSASTSAFIDTIKSLDYKSFK TIVESCGNYKVTKGKPVKGAWNIGQQRSVLTPLCGFPSQAAGVIRSIFAR TLDAANHSIPDLQRAAVTILDGISEQSLRLVDAMVYTSDLLTNSVIIMAY VTGGLVQQTSQWLSNLLGTTVEKLRPIFEWIEAKLSAGVEFLKDAWEILK FLITGVFDIVKGQIQVASDNIKDCVKCFIDVVNKALEMCIDQVTIAGAKL RSLNLGEVFIAOSKGLYRQCIRGKEQLQLLMPLKAPKEVTFLEGDSHDTV LTSEEVVLKNGELEALETPVDSFTNGAIVGTPVCVNGLMLLEIKDKEQYC ALSPGLLATNNVFRLKGGAPIKGVTFGEDTVWEVQGYKNVRITFELDERV DKVLNEKCSVYTVESGTEVTEFACVVAEAVVKTLQPVSDLLTNMGIDLDE WSVATFYLFDDAGEENFSSRMYCSFYPPDEEEEDDAECEEEEIDETCKHE YGTEDDYOGLPLEFGASAETVRVEEEEEEDWLDDTTEQSEIEPEPEPTPE EPVNQFTGYLKLTDNVAIKCVDIVKEAQSANPMVIVNAANIHLKHGGGVA GALNKATNGAMQKESDDYIKLNGPLTVGGSCLLSGHNLAKKCLHVVG**PNL** NAGEDIQLLKAAYENFNSQDILLAPLLSAGIFGAKPLQSLQVCVQTVRTQ VYIAVNDKALYEQVVMDYLDNLKPRVEAPKQEEPPNTEDSKTEEKSVVQK PVDVKPKIKACIDEVTTTLEETKFLTNKLLLFADINGKLYHDSQNMLRGE DMSFLEKDAPYMVGDVITSGDITCVVIPSKKAGGTTEMLSRALKKVPVDE YITTYPGQGCAGYTLEEAKTALKKCKSAFYVLPSEAPNAKEEILGTVSWN LREMLAHAEETRKLMPICMDVRAIMATIQRKYKGIKIQEGIVDYGVRFFF YTSKEPVASIITKLNSLNEPLVTMPIGYVTHGFNLEEAARCMRSLKAPAV VSVSSPDAVTTYNGYLTSSSKTSEEHFVETVSLAGSYRDWSYSGORTELG VEFLKRGDKIVYHTLESPVEFHLDGEVLSLDKLKSLLSLREVKTIKVFTT VDNTNLHTQLVDMSMTYGQQFGPTYLDGADVTKIKPHVNHEGKTFFVLPS DDTLRSEAFEYYHTLDESFLGRYMSALNHTKKWKFPQVGGLTSIKWADNN CYLSSVLLALQQLEVKFNAPALQEAYYRARAGDAANFCALILAYSNKTVG ELGDVRETMTHLLQHANLESAKRVLNVVCKHCGQKTTTLTGVEAVMYMGT LSYDNLKTGVSIPCVCGRDATQYLVQQESSFVMMSAPPAEYKLQQGTFLC ANEYTGNYQCGHYTHITAKETLYRIDGAHLTKMSEYKGPVTDVFYKETSY TTTIKPVSYKLDGVTYTEIEPKLDGYYKKDNAYYTEQPIDLVPTQPLPNA SFDNFKLTCSNTKFADDLNQMTGFTKPASRELSVTFFPDLNGDVVAIDYR HYSASFKKGAKLLHKPIVWHINQATTKTTFKPNTWCLRCLWSTKPVDTSN  ${\tt SFEVLAVEDTQGMDNLACESQQPTSEEVVENPTIQKEVIECDVKTTEVVG}$ NVILKPSDEGVKVTQELGHEDLMAAYVENTSITIKKPNELSLALGLKTIA THGIAAINSVPWSKILAYVKPFLGQAAITTSNCAKRLAQRVFNNYMPYVF TLLFOLCTFTKSTNSRIRASLPTTIAKNSVKSVAKLCLDAGINYVKSPKF SKLFTIAMWLLLLSICLGSLICVTAAFGVLLSNFGAPSYCNGVRELYLNS SNVTTMDFCEGSFPCSICLSGLDSLDSYPALETIQVTISSYKLDLTILGL AAEWVLAYMLFTKFFYLLGLSAIMQVFFGYFASHFISNSWLMWFIISIVQ MAPVSAMVRMYIFFASFYYIWKSYVHIMDGCTSSTCMMCYKRNRATRVEC TTIVNGMKRSFYVYANGGRGFCKTHNWNCLNCDTFCTGSTFISDEVARDL SLQFKRPINPTDQSSYIVDSVAVKNGALHLYFDKAGQKTYERHPLSHFVN LDNLRANNTKGSLPINVIVFDGKSKCDESASKSASVYYSQLMCQPILLLD QALVSDVGDSTEVSVKMFDAYVDTFSATFSVPMEKLKALVATAHSELAKG VALDGVLSTFVSAARQGVVDTDVDTKDVIECLKLSHHSDLEVTGDSCNNF MLTYNKVENMTPRDLGACIDCNARHINAQVAKSHNVSLIWNVKDYMSLSE QLRKQIRSAAKKNNIPFRLTCATTRQVVNVITTKISLKGGKIVSTCFKLM LKATLLCVLAALVCYIVMPVHTLSIHDGYTNEIIGYKAIQDGVTRDIIST DDCFANKHAGFDAWFSQRGGSYKNDKSCPVVAAIITREIGFIVPGLPGTV LRAINGDFLHFLPRVFSAVGNICYTPSKLIEYSDFATSACVLAAECTIFK DAMGKPVPYCYDTNLLEGSISYSELRPDTRYVLMDGSIIQFPNTYLEGSV RVVTTFDAEYCRHGTCERSEVGICLSTSGRWVLNNEHYRALSGVFCGVDA MNLIANIFTPLVQPVGALDVSASVVAGGIIAILVTCAAYYFMKFRRVFGE YNHVVAANALLFLMSFTILCLVPAYSFLPGVYSVFYLYLTFYFTNDVSFL AHLOWFAMFSPIVPFWITAIYVFCISLKHCHWFFNNYLRKRVMFNGVTFS TFEEAALCTFLLNKEMYLKLRSETLLPLTQYNRYLALYNKYKYFSGALDT TSYREAACCHLAKALNDFSNSGADVLYQPPQTSITSAVLQSGFRKMAFPS GKVEGCMVQVTCGTTTLNGLWLDDTVYCPRHVICTAEDMLNPNYEDLLIR KSNHSFLVQAGNVQLRVIGHSMQNCLLRLKVDTSNPKTPKYKFVRIQPGQ TFSVLACYNGSPSGVYQCAMRPNHTIKGSFLNGSCGSVGFNIDYDCVSFC YMHHMELPTGVHAGTDLEGKFYGPFVDRQTAQAAGTDTTITLNVLAWLYA AVINGDRWFLNRFTTTLNDFNLVAMKYNYEPLTQDHVDILGPLSAQTGIA VLDMCAALKELLQNGMNGRTILGSTILEDEFTPFDVVRQCSGVTFQGKFK 52/55

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KIVKGTHHWMLLTFLTSLLILVQSTQWSLFFFVYENAFLPFTLGIMAIAA CAMLLVKHKHAFLCLFLLPSLATVAYFNMVYMPASWVMRIMTWLELADTS LSGYRLKDCVMYASALVLLILMTARTVYDDAARRVWTLMNVITLVYKVYY GNALDQAISMWALVISVTSNYSGVVTTIMFLARAIVFVCVEYYPLLFITG NTLQCIMLVYCFLGYCCCCYFGLFCLLNRYFRLTLGVYDYLVSTQEFRYM NSQGLLPPKSSIDAFKLNIKLLGIGGKPCIKVATVQSKMSDVKCTSVVLL  ${\tt SVLQQLRVESSSKLWAQCVQLHNDILLAKDTTEAFEKMVSLLSVLLSMQG}$ AVDINRLCEEMLDNRATLQAĮĄSEFSSLPSYAAYATAQEAYEQAVANGDS EVVLKKLKKSLNVAKSEFDRDAAMQRKLEKMADQAMTQMYKQARSEDKRA KVTSAMQTMLFTMLRKLDNDALNNIINNARDGCVPLNIIPLTTAAKLMVV VPDYGTYKNTCDGNTFTYASALWEIQQVVDADSKIVQLSEINMDNSPNLA WPLIVTALRANSAVKLONNELSPVALROMSCAAGTTQTACTDDNALAYYN NSKGGRFVLALLSDHQDLKWARFPKSDGTGTIYTELEPPCRFVTDTPKGP KVKYLYFIKGLNNLNRGMVLGSLAATVRLQAGNATEVPANSTVLSFCAFA VDPAKAYKDYLASGGQPITNCVKMLCTHTGTGQAITVTPEANMDQESFGG ASCCLYCRCHIDHPNPKGFCDLKGKYVQIPTTCANDPVGFTLRNTVCTVC GMWKGYGCSCDQLREPLMQSADASTF

(SEQ ID NO: 64)

**FKRVCG** 

VSAARLTPCGTGTSTDVVYRAFDIYNEKVAGFAKFLKTNCCRFQEKDE**E**G NLLDSYFVVKRHTMSNYQHEETIYNLVKDCPAVAVHDFFKFRVDGDMVPH ISRQRLTKYTMADLVYALRHFDEGNCDTLKEILVTYNCCDDDYFNKKDWY DFVENPDILRVYANLGERVRQSLLKTVQFCDAMRDAGIVGVLTLDNQDLN GNWYDFGDFVQVAPGCGVPIVDSYYSLLMPILTLTRALAAESHMDADLAK PLIKWDLLKYDFTEERLCLFDRYFKYWDQTYHPNCINCLDDRCILHCANF NVLFSTVFPPTSFGPLVRKIFVDGVPFVVSTGYHFRELGVVHNQDVNLHS SRLSFKELLVYAADPAMHAASGNLLLDKRTTCFSVAALTNNVAFQTVKPG NFNKDFYDFAVSKGFFKEGSSVELKHFFFAQDGNAAISDYDYYRYNLPTM CDIRQLLFVVEVVDKYFDCYDGGCINANQVIVNNLDKSAGFPFNKWGKAR LYYDSMSYEDQDALFAYTKRNVIPTITQMNLKYAISAKNRARTVAGVSIC STMTNRQFHQKLLKSIAATRGATVVIGTSKFYGGWHNMLKTVYSDVETPH LMGWDYPKCDRAMPNMLRIMASLVLARKHNTCCNLSHRFYRLANECAQVL SEMVMCGGSLYVKPGGTSSGDATTAYANSVFNICQAVTANVNALLSTDGN KIADKYVRNLQHRLYECLYRNRDVDHEFVDEFYAYLRKHFSMMILSDDAV VCYNSNYAAQGLVASIKNFKAVLYYQNNVFMSEAKCWTETDLTKGPHEFC SQHTMLVKQGDDYVYLPYPDPSRILGAGCFVDDIVKTDGTLMIERFVSLA IDAYPLTKHPNQEYADVFHLYLQYIRKLHDELTGHMLDMYSVMLTNDNTS RYWEPEFYEAMYTPHTVLQAVGACVLCNSQTSLRCGACIRRPFLCCKCCY DHVISTSHKLVLSVNPYVCNAPGCDVTDVTQLYLGGMSYYCKSHKPPISF PLCANGQVFGLYKNTCVGSDNVTDFNAIATCDWTNAGDYILANTCTERLK LFAAETLKATEETFKLSYGIATVREVLSDRELHLSWEVGKPRPPLNRNYV FTGYRVTKNSKVQIGEYTFEKGDYGDAVVYRGTTTYKLNVGDYFVLTSHT VMPLSAPTLVPQEHYVRITGLYPTLNISDEFSSNVANYQKVGMQKYSTLQ GPPGTGKSHFAIGLALYYPSARIVYTACSHAAVDALCEKALKYLPIDKCS RIIPARARVECFDKFKVNSTLEQYVFCTVNALPETTADIVVFDEISMATN  $\verb|VDLSVVNARLRAKHYVYIGDPAQLPAPRTLLTKGTLEPEYFNSVCRLMKT|\\$ IGPDMFLGTCRRCPAEIVDTVSALVYDNKLKAHKDKSAQCFKMFYKGVIT HDVSSAINRPQIGVVREFLTRNPAWRKAVFISPYNSQNAVASKILGLPTQ TVDSSQGSEYDYVIFTQTTETAHSCNVNRFNVAITRAKIGILCIMSDRDL YDKLQFTSLEIPRRNVATLQAENVTGLFKDCSKIITGLHPTQAPTHLSVD IKFKTEGLCVDIPGIPKDMTYRRLISMMGFKMNYQVNGYPNMPITREEAI RHVRAWIGFDVEGCHATRDAVGTNLPLQLGFSTGVNLVAVPTGYVDTENN TEFTRVNAKPPPGDQFKHLIPLMYKGLPWNVVRIKIVQMLSDTLKGLSDR VVFVLWAHGFELTSMKYFVKIGPERTCCLCDKRATCFSTSSDTYACWNHS VGFDYVYNPFMIDVQQWGFTGNLQSNHDQHCQVHGNAHVASCDAIMTRCL AVHECFVKRVDWSVEYPIIGDELRVNSACRKVQHMVVKSALLADKFPVLH DIGNPKAIKCVPQAEVEWKFYDAQPCSDKAYKIEELFYSYATHHDKFTDG VCLFWNCNVDRYPANAIVCRFDTRVLSNLNLPGCDGGSLYVNKHAFHTPA FDKSAFTNLKQLPFFYYSDSPCESHGKQVVSDIDYVPLKSATCITRCNLG GAVCRHHANEYRQYLDAYNMMISAGFSLWIYKQFDTYNLWNTFTRLQSLE NVAYNVVNKGHFDGHAGEAPVSIINNAVYTKVDGIDVEIFENKTTLPVNV AFELWAKRNIKPVPEIKILNNLGVDIAANTVIWDYKREAPAHVSTIGVCT MTDIAKKPTESACSSLTVLFDGRVEGQVDLFRNARNGVLITEGSVKGLTP SKGPAOASVNGVTLIGESVKTQFNYFKKVDGIIQQLPETYFTQSRDLEDF KPRSQMETDFLELAMDEFIQRYKLEGYAFEHIVYGDFSHGQLGGLHLMIG LAKRSQDSPLKLEDFIPMDSTVKNYFITDAQTGSSKCVCSVIDLLLDDFV EIIKSQDLSVISKVVKVTIDYAEISFMLWCKDGHVETFYPKLQASQAWQP GVAMPNLYKMQRMLLEKCDLQNYGENAVIPKGIMMNVAKYTQLCQYLNTL TLAVPYNMRVIHFGAGSDKGVAPGTAVLRQWLPTGTLLVDSDLNDFVSDA DSTLIGDCATVHTANKWDLIISDMYDPRTKHVTKENDSKEGFFTYLCGFI KOKLALGGSIAVKITEHSWNADLYKLMGHFSWWTAFVTNVNASSSEAFLI GANYLGKPKEQIDGYTMHANYIFWRNTNPIQLSSYSLFDMSKFPLKLRGT AVMSLKENQINDMIYSLLEKGRLIIRENNRVVVSSDILVNN

(SEQ ID NO: 65)

FIGURE 17

MDLFMRFFTLRSITAQPVKIDNASPASTVHATATIPLQASLPFGWLVIGV AFLAVFQSATKIIALNKRWQLALYKGFQFICNLLLLFVTIYSHLLLVAAG MEAQFLYLYALIYFLQCINACRIIMRCWLCWKCKSKNPLLYDANYFVCWH THNYDYCIPYNSVTDTIVVTEGDGISTPKLKEDYQIGGYSEDRHSGVKDY VVVHGYFTEVYYQLESTQITTDTGIENATFFIFNKLVKDPPNVQIHTIDG SSGVANPAMDPIYDEPTTTTSVPL (SEQ ID NO: 66)

#### FIGURE 18

MMPTTLFAGTHITMTTVYHITVSQIQLSLLKVTAFQHQNSKKTTKLVVIL RIGTQVLKTMSLYMAISPKFTTSLSLHKLLQTLVLKMLHSSSLTSLLKTH RMCKYTQSTALQELLIQQWIQFMMSRRRLLACLCKHKKVSTNLCTHSFRK KQVR (SEQ ID NO: 67)

#### FIGURE 19

MFHLVDFQVTIAEILIIIMRTFRIAIWNLDVIISSIVRQLFKPLTKKNYS ELDDEEPMELDYP (SEQ ID NO: 68)

#### FIGURE 20

MKIILFLTLIVFTSCELYHYQECVRGTTVLLKEPCPSGTYEGNSPFHPLA DNKFALTCTSTHFAFACADGTRHTYQLRARSVSPKLFIRQEEVQQELYSP LFLIVAALVFLILCFTIKRKTE (SEQ ID NO: 69)

#### FIGURE 21

MNELTLIDFYLCFLAFLLFLVLIMLIIFWFSLEIQDLEEPCTKV

(SEQ ID NO: 70)

#### FIGURE 22

MKLLIVLTCISLCSCICTVVQRCASNKPHVLEDPCKVQH

(SEQ ID NO: 71)

#### FIGURE 23

MCLKILVRYNTRGNTYSTAWLCALGKVLPFHRWHTMVQTCTPNVTINCQD PAGGALIARCWYLHEGHQTAAFRDVLVVLNKRTN (SEQ ID NO: 72)

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## FIGURE 24

MDPNQTNVVPPALHLVDPQIQLTITRMEDAMGQGQNSADPKVYPIILRLG SQLSLSMARRNLDSLEARAFQSTPIVVQMTKLATTEELPDEFVVVTAK

(SEQ ID NO: 73)

FIGURE 25

MLPPCYNFLKEQHCQKASTQREAEAAVKPLLAPHHVVAVIQEIQLLAAVG EILLLEWLAEVVKLPSRYCC (SEQ ID NO: 74)

### FIGURE 26

CIAVGQLCVFWNIGRPCCSGLCVFA--CTVKL CISLCS-CICTVVQRCASNKPHVLEDPCKVQH \*\*::. \*: : \* ... \*: \*.\*: conotoxin sars

FIGURE 27

# JC06 Rec'd PCT/PTO 28 OCT 2005 10/55507p3r/CA2004/000626

### WO 2004/096842

## SEQUENCE LISTING

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His	Thr	Ser 35	Ser	Met	Arg	Gly	Val 40	Tyr	Tyr	Pro	Asp	Glu 45	İle	Phe	Arg
Ser	Asp 50	Thr	Leu	Tyr	Leu	Thr 55	Gln	Asp	Leu	Phe	Leu 60	Pro	Phe	Tyr.	Ser
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Asn	Phe 130	Glu	Leu	Cys	Asp	Asn 135	Pro	Phe	Phe	Ala	Val 140	Ser	Lys	·Pro	Met
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- Gly Ile Asn Ile Thr Asn Phe Arg Ala Ile Leu Thr Ala Phe Ser Pro 225 230 235 240
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410 .

415

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Ser Val Arg Asp Pro Lys Thr Ser Glu Ile Leu Asp Ile Ser Pro Cys 565 570 575

Ala Phe Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Ala Ser Ser 580 585 590

Glu Val Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Asp Val Ser Thr 595 600 605

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His Val Asp Thr Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile 645 650 655

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Cys		Gln 835	Lys	Phe	Asn	Gly	Leu 840		Val	Leu	Pro	Pro 845	Leu	Leu	.Thr
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Ile Ser Gln Ile Gln Glu Ser Leu Thr Thr Thr Ser Thr Ala Leu Gly 920 915 925

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- Met Ala Asp Asn Gly Thr Ile Thr Val Glu Glu Leu Lys Gln Leu Leu 10
- Glu Gln Trp Asn Leu Val Ile Gly Phe Leu Phe Leu Ala Trp Ile Met . 25
- Leu Leu Gln Phe Ala Tyr Ser Asn Arg Asn Arg Phe Leu Tyr Ile Ile . 35
- Lys Leu Val Phe Leu Trp Leu Leu Trp Pro Val Thr Leu Ala Cys Phe 55
- Val Leu Ala Ala Val Tyr Arg Ile Asn Trp Val Thr Gly Gly Ile Ala 75

Ile Ala Met Ala Cys Ile Val Gly Leu Met Trp Leu Ser Tyr Phe Val 85 90 95

- Ala Ser Phe Arg Leu Phe Ala Arg Thr Arg Ser Met Trp Ser Phe Asn 100 105 110
- Pro Glu Thr Asn Ile Leu Leu Asn Val Pro Leu Arg Gly Thr Ile Val 115 120 125
- Thr Arg Pro Leu Met Glu Ser Glu Leu Val Ile Gly Ala Val Ile Ile 130 135 140
- Arg Gly His Leu Arg Met Ala Gly His Ser Leu Gly Arg Cys Asp Ile 145 150 155 160
- Lys Asp Leu Pro Lys Glu Ile Thr Val Ala Thr Ser Arg Thr Leu Ser 165 170 175
- Tyr Tyr Lys Leu Gly Ala Ser Gln Arg Val Gly Thr Asp Ser Gly Phe.
  180 185 190
- Ala Ala Tyr Asn Arg Tyr Arg Ile Gly Asn Tyr Lys Leu Asn Thr Asp 195 200 205
- His Ala Gly Ser Asn Asp Asn Ile Ala Leu Leu Val 210 215 220
- <210> 35
- <211> 76
- <212> PRT
- <213> Severe acute respiratory syndrome virus
- <400> 35
- Met Tyr Ser Phe Val Ser Glu Glu Thr Gly Thr Leu Ile Val Asn Ser 1 5 10 15
- Val Leu Leu Phe Leu Ala Phe Val Val Phe Leu Leu Val Thr Leu Ala 20 25 30
- Ile Leu Thr Ala Leu Arg Leu Cys Ala Tyr Cys Cys Asn Ile Val Asn 35 40 45
- Val Ser Leu Val Lys Pro Thr Val Tyr Val Tyr Ser Arg Val Lys Asn 50 55 60

Leu Asn Ser Ser Glu Gly Val Pro Asp Leu Leu Val 65 70 75

<210> 36 ·

<211> 422

<212> PRT

<213> Severe acute respiratory syndrome virus

<400> 36

Met Ser Asp Asn Gly Pro Gln Ser Asn Gln Arg Ser Ala Pro Arg Ile
1 5 10 15

Thr Phe Gly Gly Pro Thr Asp Ser Thr Asp Asn Asn Gln Asn Gly Gly 20 25 30

Arg Asn Gly Ala Arg Pro Lys Gln Arg Pro Gln Gly Leu Pro Asn 35 40

Asn Thr Ala Ser Trp Phe Thr Ala Leu Thr Gln His Gly Lys Glu Glu 50 55 60

Leu Arg Phe Pro Arg Gly Gln Gly Val Pro Ile Asn Thr Asn Ser Gly 65 70 75 80

Pro Asp Asp Gln Ile Gly Tyr Tyr Arg Arg Ala Thr Arg Arg Val Arg 85 90 95

Gly Gly Asp Gly Lys Met Lys Glu Leu Ser Pro Arg Trp Tyr Phe Tyr 100 105 110

Tyr Leu Gly Thr Gly Pro Glu Ala Ser Leu Pro Tyr Gly Ala Asn Lys 115 120 125

Glu Gly Ile Val Trp Val Ala Thr Glu Gly Ala Leu Asn Thr Pro Lys 130 135 140

Asp His Ile Gly Thr Arg Asn Pro Asn Asn Asn Ala Ala Thr Val Leu 145 150 155 160

Gln Leu Pro Gln Gly Thr Thr Leu Pro Lys Gly Phe Tyr Ala Glu Gly 165 170 175

Ser Arg Gly Gly Ser Gln Ala Ser Ser Arg Ser Ser Ser Arg Ser Arg 180 185 190

Gly Asn Ser Arg Asn Ser Thr Pro Gly Ser Ser Arg Gly Asn Ser Pro 195 200 205

Ala Arg Met Ala Ser Gly Gly Gly Glu Thr Ala Leu Ala Leu Leu Leu 210 215 220 Leu Asp Arg Leu Asn Gln Leu Glu Ser Lys Val Ser Gly Lys Gly Gln 235 240 Gln Gln Gln Gly Gln Thr Val Thr Lys Lys Ser Ala Ala Glu Ala Ser 245 250 255 Lys Lys Pro Arg Gln Lys Arg Thr Ala Thr Lys Gln Tyr Asn Val Thr 260 265 Gln Ala Phe Gly Arg Arg Gly Pro Glu Gln Thr Gln Gly Asn Phe Gly 280 285 Asp Gln Asp Leu Ile Arg Gln Gly Thr Asp Tyr Lys His Trp Pro Gln 290 295 300 Ile Ala Gln Phe Ala Pro Ser Ala Ser Ala Phe Phe Gly Met Ser Arg 310 315 320 Ile Gly Met Glu Val Thr Pro Ser Gly Thr Trp Leu Thr Tyr His Gly 330 335 . 325 Ala Ile Lys Leu Asp Asp Lys Asp Pro Gln Phe Lys Asp Asn Val Ile 340 345 Leu Leu Asn Lys His Ile Asp Ala Tyr Lys Thr Phe Pro Pro Thr Glu 355 . 360 Pro Lys Lys Asp Lys Lys Lys Thr Asp Glu Ala Gln Pro Leu Pro 370 375 380 Gln Arg Gln Lys Lys Gln Pro Thr Val Thr Leu Leu Pro Ala Ala Asp 390 385 395 Met Asp Asp Phe Ser Arg Gln Leu Gln Asn Ser Met Ser Gly Ala Ser 405 410 415 Ala Asp Ser Thr Gln Ala 420

<210> 37 <211> 230 <212> PRT <213> Bovine coronavirus

<400> 37

Met Ser Ser Val Thr Thr Pro Ala Pro Val Tyr Thr Trp Thr Ala Asp
1 5 10 . 15

Glu Ala Ile Lys Phe Leu Lys Glu Trp Asn Phe Ser Leu Gly Ile Ile 20 25 30

Leu Leu Phe Ile Thr Val Ile Leu Gln Phe Gly Tyr Thr Ser Arg Ser 35 40 45

Met Phe Val Tyr Val Ile Lys Met Val Ile Leu Trp Leu Met Trp Pro 50 55 60

Leu Thr Ile Ile Leu Thr Ile Phe Asn Cys Val Tyr Ala Leu Asn Asn 65 70 75 80

Val Tyr Leu Gly Phe Ser Ile Val Phe Thr Ile Val Ala Ile Ile Met 85 90 95

Trp Ile Val Tyr Phe Val Asn Ser Ile Arg Leu Phe Ile Arg Thr Gly 100 105 110

Ser Trp Trp Ser Phe Asn Pro Glu Thr Asn Asn Leu Met Cys Ile Asp 115 120 125

Met Lys Gly Arg Met Tyr Val Arg Pro Ile Ile Glu Asp Tyr His Thr 130 135 140

Leu Thr Val Thr Ile Ile Arg Gly His Leu Tyr Met Gln Gly Ile Lys
145 150 155 160

Leu Gly Thr Gly Tyr Ser Leu Ser Asp Leu Pro Ala Tyr Val Thr Val 165 170 175

Ala Lys Val Ser His Leu Leu Thr Tyr Lys Arg Gly Phe Leu Asp Lys 180 185 190

Ile Gly Asp Thr Ser Gly Phe Ala Val Tyr Val Lys Ser Lys Val Gly
195 200 205

Asn Tyr Arg Leu Pro Ser Thr Gln Lys Gly Ser Gly Leu Asp Thr Ala 210 215 220

Leu Leu Arg Asn Asn Ile

<210> 38 <211> 226 <212> PRT <213> Avian infectious bronchitis virus

230

<400> 38

Met Ser Asn Gly Thr Glu Asn Cys Thr Leu Ser Thr Gln Gln Ala Ala 5 · 10

Glu Leu Phe Lys Glu Tyr Asn Leu Phe Ile Thr Ala Phe Leu Leu Phe 20 25

Leu Thr Ile Leu Leu Gln Tyr Gly Tyr Ala Thr Arg Ser Arg Phe Ile 35 40 45

Tyr Ile Leu Lys Met Ile Val Leu Trp Cys Phe Trp Pro Leu Asn Ile 55 60

Ala Val Gly Ile Ile Ser Cys Ile Tyr Pro Pro Asn Thr Gly Gly Leu. 75 . 70

Val Ala Ala Ile Ile Leu Thr Val Phe Ala Cys Leu Ser Phe Val Gly 85 90 95

Tyr Trp Ile Gln Ser Phe Arg Leu Phe Lys Arg Cys Arg Ser Trp Trp 100 105 110

Ser Phe Asn Pro Glu Ser Asn Ala Val Gly Ser Ile Leu Leu Thr Asn 115 120 125

Gly Gln Gln Cys Asn Phe Ala Ile Glu Ser Val Pro Met Val Leu Ser 130

Pro Ile Ile Lys Asn Gly Ala Leu Tyr Cys Glu Gly Gln Trp Leu Ala 150 155

Lys Cys Glu Pro Asp His Leu Pro Lys Asp Ile Phe Val Cys Thr Pro 165 170 -

Asp Arg Arg Asn Ile Tyr Arg Met Val Gln Lys Tyr Thr Gly Asp Gln

Ser Gly Asn Lys Lys Arg Phe Ala Thr Phe Val Tyr Ala Lys Gln Ser

Val Asp Thr Gly Glu Leu Gly Ser Val Ala Thr Gly Gly Ser Ser Leu 210 215 220

Tyr Thr 225

<210> 39 .

· <211> 262

<212> PRT

<213> Transmissible gastroenteritis virus

<400> .39

Met Lys Ile Leu Leu Ile Leu Ala Cys Val Ile Ala Cys Ala Cys Gly 1 5 10 15

Glu Arg Tyr Cys Ala Met Lys Ser Asp Thr Asp Leu Ser Cys Arg Asn 20 25 30

Ser Thr Ala Ser Asp Cys Glu Ser Cys Phe Asn Gly Gly Asp Leu Ile 35 40 45

Trp His Leu Ala Asn Trp Asn Phe Ser Trp Ser Ile Ile Leu Ile Val 50 55 60

Phe Ile Thr Val Leu Gln Tyr Gly Arg Pro Gln Phe Ser Trp Phe Val 65 70 75 80

Tyr Gly Ile Lys Met Leu Ile Met Trp Leu Leu Trp Pro Val Val Leu 85 90 95

Ala Leu Thr Ile Phe Asn Ala Tyr Ser Glu Tyr Gln Val Ser Arg Tyr 100 105 110

Val Met Phe Gly Phe Ser Ile Ala Gly Ala Ile Val Thr Phe Val Leu 115 120 125

Trp Ile Met Tyr Phe Val Arg Ser Ile Gln Leu Tyr Arg Arg Thr Lys
130 140

Ser Trp Trp Ser Phe Asn Pro Glu Thr Lys Ala Ile Leu Cys Val Ser 145 155 160

Ala Leu Gly Arg Ser Tyr Val Leu Pro Leu Glu Gly Val Pro Thr Gly
165 170 175

Val Thr Leu Thr Leu Leu Ser Gly Asn Leu Tyr Ala Glu Gly Phe Lys

185

190

Ile Ala Gly Gly Met Asn Ile Asp Asn Leu Pro Lys Tyr Val Met Val 195 200 205

Ala Leu Pro Ser Arg Thr Ile Val Tyr Thr Leu Val Gly Lys Lys Leu 215 220

Lys Ala Ser Ser Ala Thr Gly Trp Ala Tyr Tyr Val Lys Ser Lys Ala 230 235 . 240

Gly Asp Tyr Ser Thr Glu Ala Arg Thr Asp Asn Leu Ser Glu Gln Glu 245 250

Lys Leu Leu His Met Val 260

<210> 40 ·

<211> 263
<212> PRT
<213> feline coronavirus

Met Lys Ile Leu Leu Ile Leu Ala Cys Ala Val Ala Cys Val Tyr Gly 5 10

Glu Gln Ile Arg Tyr Cys Ala Met Gln Glu Thr Gly Leu Ser Cys Arg 20 25

Asn Gly Thr Ala Ser Asp Cys Glu Ser Cys Phe Asn Gly Gly Asp Leu 35 40 45

Ile Trp His Leu Ala Asn Trp Asn Phe Ser Trp Ser Ile Ile Leu Ile 50

Val Phe Ile Thr Val Leu Gln Tyr Gly Arg Pro Gin Phe Ser Trp Phe

Val Tyr Gly Ile Lys Met Leu Ile Met Trp Leu Leu Trp Pro Ile Val 85 90

Leu Ala Leu Thr Ile Phe Asn Ala Tyr Ser Glu Tyr Glu Val Ser Arg 105

Tyr Val Met Phe Gly Phe Ser Val Ala Gly Ala Val Val Thr Phe Ala 120 125

Leu Trp Met Met Tyr Phe Val Arg Ser Ile Gln Leu Tyr Arg Arg Thr
130 135 140

Lys Ser Trp Trp Ser Phe Asn Pro Glu Thr Asn Ala Ile Leu Cys Val 145 150 155 160

Asn Ala Leu Gly Arg Ser Tyr Val Leu Pro Leu Asp Gly Thr Pro Thr 165 170 175

Gly Val Thr Leu Thr Leu Leu Ser Gly Asn Leu Tyr Ala Glu Gly Phe 180 185 190

Lys Met Ala Gly Gly Leu Thr Ile Glu His Leu Pro Lys Tyr Val Met 195 200 205

Ile Arg Thr Pro Asn Arg Thr Ile Val Tyr Thr Leu Val Gly Lys Gln 210 215 220

Leu Lys Ala Thr Thr Ala Thr Gly Trp Ala Tyr Tyr Val Lys Ser Lys 225 230 235 240

Ala Gly Asp Tyr Ser Thr Glu Ala Arg Thr Asp Asn Leu Ser Glu His
245 250 255

Glu Lys Leu Leu His Met Val 260

<210> 41

<211> 231

<212> PRT

<213> Human coronavirus OC43

MSSKTTPAPVYIWTADEAIKFLKEWNFSLGIILLFITIILQFGYTSRSMFVYVIKMIILWLMWPLTIILTIFNCVY ALNNVYLGLSIVFTIVAIIMWIVYFVNSIRLFIRTGSFWSFNPETNNLMCIDMKGTMYVRPIIEDYHTLTVTIIRG HLYIQGIKLGTGYSWADLPAYMTVAKVTHLCTYKRGFLDRISDTSGFAVYVKSKVGNYRLPSTQKGSGMDTALLRN NI

<SEQ ID NO:37;prt;Porcine hemagglutinating encephalomyelitis virus</pre>

<400> 41

Met Ser Ser Pro Thr Thr Pro Val Pro Val Ile Ser Trp Thr Ala Asp 1 5 10 15

Glu Ala Ile Lys Phe Leu Lys Glu Trp Asn Phe Ser Leu Gly Ile Ile 20 25 30

Val Leu Phe Ile Thr Ile Ile Leu Gln Phe Gly Tyr Thr Ser Arg Ser 35 40 45

WO 2004/096842 PCT/CA2004/000626

Met Phe Val Tyr Val Ile Lys Met Val Ile Leu Trp Leu Met Trp Pro 50 55 60

Leu Thr Ile Ile Leu Thr Ile Phe Asn Cys Val Tyr Ala Leu Asn Asn 65 70 75 80

Val Tyr Leu Gly Phe Ser Ile Val Phe Thr Ile Val Ala Ile Ile Met 85 90 95

Trp Val Val Tyr Phe Val Asn Ser Ile Arg Leu Phe Ile Arg Thr Gly
100 105 110

Ser Trp Trp Ser Phe Asn Pro Glu Thr Asn Asn Leu Met Cys Ile Asp 115 120 125

Met Lys Gly Arg Met Tyr Val Arg Pro Ile Ile Glu Asp Tyr His Thr 130 135 140

Leu Thr Ala Thr Ile Ile Arg Gly His Leu Tyr Ile Gln Gly Ile Lys 145 150 155 160

Leu Gly Thr Gly Tyr Ser Leu Ser Asp Leu Pro Ala Tyr Val Thr Val 165 170 175

Ala Lys Val Thr His Leu Cys Thr Tyr Lys Arg Gly Phe Leu Asp Arg 180 185 190

Ile Gly Asp Thr Ser Gly Phe Ala Val Tyr Val Lys Ser Lys Val Gly
195 200 205

Asn Tyr Arg Leu Pro Ser Thr His Lys Gly Ser Gly Met Asp Thr Ala 210 215 220

Leu Leu Arg Asn Asn Ile Met 225 230

<210> 42

<211> 223

<212> PRT

<213> Avian infectious bronchitis virus

<400> 42

Met Met Glu Asn Cys Thr Leu Asn Leu Glu Gln Ala Thr Leu Leu Phe 1 5 10 15

Lys Glu Tyr Asn Leu Phe Ile Thr Ala Phe Leu Leu Phe Leu Thr Ile

25

30

Leu Leu Gln Tyr Gly Tyr Ala Thr Arg Ser Arg Phe Ile Tyr Ile Leu. 35 40 45

Lys Met Ile Val Leu Trp Cys Phe Trp Pro Leu Asn Ile Ala Val Gly 50 55 60

Val Ile Ser Cys Ile Tyr Pro Pro Asn Thr Gly Gly Leu Val Ala Ala 65 70 75 80

Ile Ile Leu Thr Val Phe Ala Cys Leu Ser Phe Val Gly Tyr Trp Ile 85 90 95

Gln Ser Cys Arg Leu Phe Lys Arg Cys Arg Ser Trp Trp Ser Phe Asn 100 105 110

Pro Glu Ser Asn Ala Val Gly Ser Ile Leu Leu Thr Asn Gly Gln Gln 115 120 125

Cys Asn Phe Ala Ile Glu Ser Val Pro Met Val Leu Ala Pro Ile Ile 130 135 140

Lys Asn Gly Val Leu Tyr Cys Glu Gly Gln Trp Leu Ala Lys Cys Glu 145 150 155 160.

Pro Asp His Leu Pro Lys Asp Ile Phe Val Cys Thr Pro Asp Arg Arg 165 170 175

Asn Ile Tyr Arg Met Val Gln Lys Tyr Thr Gly Asp Gln Ser Gly Asn 180 185 190

Lys Lys Arg Val Ala Thr Phe Val Tyr Ala Lys Gln Ser Val Asp Thr 195 200 205

Gly Glu Leu Glu Ser Val Pro Thr Gly Gly Ser Ser Leu Tyr Thr 210 215 220

<210> 43

<211> 455

<212> PRT

<213> Mouse Hepatitis Virus

<400> 43

Met Ser Phe Val Pro Gly Gln Glu Asn Ala Gly Ser Arg Ser Ser Ser 1 5 10 15

Val Asn Arg Ala Gly Asn Gly Ile Leu Lys Lys Thr Thr Trp Ala Asp
20 25 30

- Gin Thr Glu Arg Gly Pro Asn Asn Gln Asn Arg Gly Arg Arg Asn Gln
  35 40 45
- Pro Lys Gln Thr Ala Thr Thr Gln Pro Asn Ser Gly Ser Val Val Pro 50 55 60
- His Tyr Ser Trp Phe Ser Gly Ile Thr Gln Phe Gln Lys Gly Lys Glu 65 70 75 80
- Phe Gln Phe Ala Gln Gly Gln Gly Val Pro Ile Ala Asn Gly Ile Pro . 85 90 95
- Ala Ser Glu Gln Lys Gly Tyr Trp Tyr Arg His Asn Arg Arg Ser Phe 100 105 110
- Lys Thr Pro Asp Gly Gln Gln Lys Gln Leu Leu Pro Arg Trp Tyr Phe 115 120 125
- Tyr Tyr Leu Gly Thr Gly Pro His Ala Gly Ala Glu Tyr Gly Asp Asp 130 135 140
- Ile Asp Gly Val Val Trp Val Ala Ser Gln Gln Ala Asp Thr Lys Thr
  145 150 155 160
- Thr Ala Asp Ile Val Glu Arg Asp Pro Ser Ser His Glu Ala Ile Pro 165 170 175
- Thr Arg Phe Ala Pro Gly Thr Val Leu Pro Gln Gly Phe Tyr Val Glu 180 185 190
- Gly Ser Gly Arg Ser Ala Pro Ala Ser Arg Ser Gly Ser Arg Ser Gln
  195 200 205
- Ser Arg Gly Pro Asn Asn Arg Ala Arg Ser Ser Ser Asn Gln Arg Gln 210 215 220
- Pro Ala Ser Thr Val Lys Pro Asp Met Ala Glu Glu Ile Ala Ala Leu 225 230 235 240
- Val Leu Ala Lys Leu Gly Lys Asp Ala Gly Gln Pro Lys Gln Val Thr 245 250 255

Lys Gln Ser Ala Lys Glu Val Arg Gln Lys Ile Leu Asn Lys Pro Arg 260 265 270

Gln Lys Arg Thr Pro Asn Lys Gln Cys Pro Val Gln Gln Cys Phe Gly 275 280 285

Lys Arg Gly Pro Asn Gln Asn Phe Gly Gly Ser Glu Met Leu Lys Leu 290 295 300

Gly Thr Ser Asp Pro Gln Phe Pro IIe Leu Ala Glu Leu Ala Pro Thr 305 310 315 320

Pro Ser Ala Phe Phe Phe Gly Ser Lys Leu Glu Leu Val Lys Lys Asn 325 330 335

Ser Gly Gly Ala Asp Asp Pro Thr Lys Asp Val Tyr Glu Leu Gln Tyr 340 345 350

Ser Gly Ala Ile Arg Phe Asp Ser Thr Leu Pro Gly Phe Glu Thr Ile 355 360 365

Met Lys Val Leu Asn Glu Asn Leu Asp Ala Tyr Gln Asp Gln Ala Gly 370 375

Gly Ala Asp Val Val Ser Pro Lys Pro Gln Arg Lys Arg Gly Thr Lys 385 390 395 400

Gln Lys Ala Leu Lys Gly Glu Val Asp Asn Val Ser Val Ala Lys Pro 405 410 415

Lys Ser Ser Val Gln Arg Asn Val Ser Arg Glu Leu Thr Pro Glu Asp 420 425 430

Arg Ser Leu Leu Ala Gln Ile Leu Asp Asp Gly Val Val Pro Asp Gly 435 440 445

Leu Glu Asp Asp Ser Asn Val 450 455

<210> 44

<211> 448

<212> PRT

<213> Bovine coronavirus

<400> 44

Met Ser Phe Thr Pro Gly Lys Gln Ser Ser Ser Arg Ala Ser Ser Gly 1 5 10 15

Asn Arg Ser Gly Asn Gly Ile Leu Lys Trp Ala Asp Gln Ser Asp Gln
20 25 30

WO 2004/096842

- Ser Arg Asn Val Gln Thr Arg Gly Arg Arg Ala Gln Pro Lys Gln Thr 35 40 45
- Ala Thr Ser Gln Gln Pro Ser Gly Gly Asn Val Val Pro Tyr Tyr Ser 50 55 60
- Trp Phe Ser Gly Ile Thr Gln Phe Gln Lys Gly Lys Glu Phe Glu Phe 65 70 75 80
- Ala Glu Gly Gln Gly Val Pro Ile Ala Pro Gly Val Pro Ala Thr Glu 85 90 95
- Ala Lys Gly Tyr Trp Tyr Arg His Asn Arg Arg Ser Phe Lys Thr Ala 100 105 110
- Asp Gly Asn Gln Arg Gln Leu Leu Pro Arg Trp Tyr Phe Tyr Tyr Leu 115 120 125
- Gly Thr Gly Pro His Ala Lys Asp Gln Tyr Gly Thr Asp Ile Asp Gly 130 135 140
- Val Tyr Trp Val Ala Ser Asn Gln Ala Asp Val Asn Thr Pro Ala Asp 145 150 155 160
- Ile Leu Asp Arg Asp Pro Ser Ser Asp Glu Ala Ile Pro Thr Arg Phe 165 170 175
- Pro Pro Gly Thr Val Leu Pro Gln Gly Tyr Tyr Ile Glu Gly Ser Gly 180 185 190
- Arg Ser Ala Pro Asn Ser Arg Ser Thr Ser Arg Ala Ser Ser Arg Ala 195 200 205
- Ser Ser Ala Gly Ser Arg Ser Arg Ala Asn Ser Gly Asn Arg Thr Pro 210 215 220
- Thr Ser Gly Val Thr Pro Asp Met Ala Asp Gln Ile Ala Ser Leu Val 225 230 235 240
- Leu Ala Lys Leu Gly Lys Asp Ala Ala Lys Pro Gln Gln Val Thr Lys
  245 250 255

Gln Thr Ala Lys Glu Ile Arg Gln Lys Ile Leu Asn Lys Pro Arg Gln 260 265 270

Lys Arg Ser Pro Asn Lys Gln Cys Thr Val Gln Gln Cys Phe Gly Lys 275 280 285

Arg Gly Pro Asn Gln Asn Phe Gly Gly Glu Met Leu Lys Leu Gly 290 295 300

Thr Ser Asp Pro Gln Phe Pro Ile Leu Ala Glu Leu Ala Pro Thr Ala 305 310 315 320

Gly Ala Phe Phe Phe Gly Ser Arg Leu Glu Leu Ala Lys Val Gln Asn 325 330 335

Leu Ser Gly Asn Leu Asp Glu Pro Gln Lys Asp Val Tyr Glu Leu Arg 340 345 350

Tyr Asn Gly Ala Ile Arg Phe Asp Ser Thr Leu Ser Gly Phe Glu Thr 355 360 365

Ile Met Lys Val Leu Asn Glu Asn Leu Asn Ala Tyr Gln Gln Gln Asp 370 375 380

Gly Thr Met Asn Met Ser Pro Lys Pro Gln Arg Gln Arg Gly Gln Lys 385 390 395 400

Asn Gly Gln Gly Glu Asn Asp Asn Ile Ser Val Ala Ala Pro Lys Ser 405 410 415

Arg Val Gln Gln Asn Lys Ile Arg Glu Leu Thr Ala Glu Asp Ile Ser 420 425 430

Leu Leu Lys Lys Met Asp Glu Pro Phe Thr Glu Asp Thr Ser Glu Ile
435 440 445

<210> 45

<211> 409

<212> PRT

<213> Avian infectious bronchitis virus

<400> 45

Met Ala Ser Gly Lys Ala Ala Gly Lys Thr Asp Ala Pro Ala Pro Val 1 5 10 15

Ile Lys Leu Gly Gly Pro Lys Pro Pro Lys Val Gly Ser Ser Gly Asn

Ala Ser Trp Phe Gln Ala Leu Lys Ala Lys Lys Leu Asn Ala Pro Ala.
35 40 45

Pro Lys Phe Glu Gly Ser Gly Val Pro Asp Asn Glu Asn Leu Lys Ile
50 55 60

Ser Gln Gln His Gly Tyr Trp Arg Gln Ala Arg Tyr Lys Pro Gly 65 70 75 80

Lys Gly Gly Arg Lys Pro Val Pro Asp Ala Trp Tyr Phe Tyr Tyr Thr 85 90 95

Gly Thr Gly Pro Ala Ala Asp Leu Asn Trp Gly Asp Ser Gln Asp Gly 100 105 110

Ile Val Trp Val Ala Ala Lys Gly Ala Asp Val Lys Ser Arg Ser Asn 115 120 125

Gln Gly Thr Arg Asp Pro Asp Lys Phe Asp Gln Tyr Pro Leu Arg Phe 130 135 140

Ser Asp Gly Gly Pro Asp Gly Asn Phe Arg Trp Asp Phe Ile Pro Leu 145 150 160

Asn Arg Gly Arg Ser Gly Arg Ser Thr Ala Ala Ser Ser Ala Ala Ser 165 170 175

Ser Arg Ala Pro Ser Arg Glu Gly Ser Arg Gly Arg Leu Asn Gly Ala 180 185 190

Glu Asp Asp Leu Ile Ala Arg Ala Ala Lys Ile Ile Gln Asp Gln Gln 195 200 205

Lys Lys Gly Ser Arg Ile Thr Lys Ala Lys Ala Glu Glu Met Ile His
210 215 220

Arg Arg Tyr Cys Lys Arg Thr Val Pro Pro Gly Val Ser Ile Asp Lys 225 230 235 240

Val Phe Gly Pro Arg Thr Lys Gly Lys Glu Gly Asn Phe Gly Asp Asp 245 250 255

Lys Met Asn Glu Glu Gly Ile Lys Asp Gly Arg Val Thr Ala Met Leu 260 265 270

Asn Leu Val Pro Ser Ser His Ala Cys Leu Phe Gly Ser Gln Val Thr 275 280 285

Pro Lys Leu Gln Pro Asp Gly Leu His Leu Thr Phe Arg Phe Thr Thr 290 295 300

Val Val Ser Arg Asp Asp Pro Gln Phe Asp Asn Tyr Val Lys Ile Cys 305 310 315 320

Asp Glu Cys Val Asp Gly Val Gly Thr Arg Pro Lys Asp Glu Val Val 325 330 335

Arg Pro Lys Ser Arg Ser Ser Ser Arg Pro Ala Thr Arg Gly Thr Ser 340 345 350

Pro Ala Pro Lys Gln Gln Arg Pro Lys Lys Glu Lys Lys Pro Lys Lys 355 360 365

Gln Asp Asp Glu Val Asp Lys Ala Leu Thr Ser Asp Glu Glu Arg Asn 370 380

Asn Ala Gln Leu Glu Phe Asp Asp Glu Pro Lys Val Ile Asn Trp Gly 385 390 395 400

Asp Ser Ala Leu Gly Glu Asn Glu Leu 405

<210> 46

<211> 376

<212> PRT

<213> Feline coronavirus

<400> 46

Met Ala Thr Gln Gly Gln Arg Val Asn Trp Gly Asp Glu Pro Ser Lys

1 10 15

Arg Arg Gly Arg Ser Asn Ser Arg Gly Arg Lys Asn Asn Asp Ile Pro 20 25 30

Leu Ser Tyr Phe Asn Pro Ile Thr Leu Asp Gln Gly Ser Lys Phe Trp 35 40 45

Asn Leu Cys Pro Arg Asp Phe Val Pro Lys Gly Ile Gly Asn Lys Asp 50 60

Gln 65	Gln	Ile	Gly	Tyr	Trp 70	Asn	Arg	Gln.	Ala	Arg 75	Tyr	Arģ	Ile	Val	Lys 80
Gly	Gln	Arg	Val	85	Leu	Pro	Glu <sub>.</sub>	Arg	Trp 90	Phe	Phe	Tyr	Phe	Leu 95	Gly
Thr	Gly	Pro	His 100	Ala	Asp	Ala	Lys	Phe 105	Lys	Ala	Lys	Ile	Asp 110	Gly	Val
Phe	Trp	Val 115	Ala	Arg	Asp	Gly	Ala 120	Met	Asn	Lys	Pro	Thr 125	Ser	Leu	.Gly
Thr	Arg 130	Gly	Thr	Asn	Asn	Glu 135	Ser	Lys	Pro	Leu	Lys 140	Phe	Asp	Gly	ГÀЗ
Ile 145	Prọ	Pro	Gln		Gln 150	Leu	Glu	Val	Asn	Arg 155	Ser	A'rg'	Asn	Asn	Ser . 160
Arg	Ser	Gly	Ser	Gln 165	Ser	Arg	Ser	Val	Ser 170	Arg	Asn	Arg	Ser	Gln 175	Ser
Arg	Gly	Arg	Gln 180	Glņ	Ser	Asn	Asn	Gln 185	Asn	Thr	Asn	Val	Glu 190		Thr
Ile	val	Ala 195	Val	Leu	Gln	Lys	Leu 200	Gly	Val	Thr	Asp	Lys 205	Gln	Arg	Ser,
Arg	Ser 21:0	Lys	Ser	Gly	Glu	Arg 215	Ser	Gln	Ser	ГÀЗ	Ser 220	Arg	Asp	Ţ'nr	Thr
Pro 225	Lys	Asn	Ala	Asn	Lys 230	His	Thr	Trp	Lys	Lys 235	Thr	Ala	Gly	_	Gly 240
Asp	Val	Thr	Asn	Phe 245	Tyr	Gly	Ala		Ser 250	Ser	Ser	Ala	Asn	Phe 255	Gly
Asp	Ser	Asp	Leu 260	Val	Ala	Asn	Gly	Asn 265	Ala	Ala	Lys	Суѕ	Tyr 270	Pro	Gln
Ile	Ala	Glu 275	Cys	Val	Pro	Ser	Val 280	Ser	Ser	Ile	Leu	Phe 285	Gly	Ser	Gln
Trp	Ser 290	Ala	Glu	Glu	Ala	Gly 295	Asp	Gln	Val	Lys	Val 300	Thr	Leu	Thr	His
Asn	Tyr	Tyr	Leu	Pro	Lys	Asp	Asp	Ala	Lys	Thr	Ser	Gln	Phe	Leu	Glu

305 310 315 320

Gln Ile Asp Ala Tyr Lys Arg Pro Ser Glu Val Ala Lys Asp Gln Arg. 325 330 335

Gln Arg Lys Ser Arg Ser Lys Ser Ala Asp Lys Lys Pro Glu Glu Leu 340 345 350

Ser Val Thr Leu Glu Ala Tyr Thr Asp Val Phe Asp Asp Thr Gln Val 355 360 365

Glu Met Ile Asp Glu Val Thr Asn 370 375

<210> 47 <211> 382

<211> 382 <212> PRT

<213> porcine transmissible gastroenteritis virus

<400> 47

Met Ala Asn Gln Gly Gln Arg Val Ser Trp Gly Asp Glu Ser Thr Lys
1 5 10 15

Thr Arg Gly Arg Ser Asn Ser Arg Gly Arg Lys Asn Asn Asn Ile Pro 20 25 30

Leu Ser Phe Phe Asn Pro Ile Thr Leu Gln Gln Gly Ser Lys Phe Trp 35 40 45

Asn Leu Cys Pro Arg Asp Phe Val Pro Lys Gly Ile Gly Asn Arg Asp 50 55 60

Gln Gln Ile Gly Tyr Trp Asn Arg Gln Thr Arg Tyr Arg Met Val Lys 65 70 75 80

Gly Gln Arg Lys Glu Leu Pro Glu Arg Trp Phe Phe Tyr Tyr Leu Gly 85 90 95

Thr Gly Pro His Ala Asp Ala Lys Phe Lys Asp Lys Leu Asp Gly Val

Val Trp Val Ala Lys Asp Gly Ala Met Asn Lys Pro Thr Thr Leu Gly 115 120 125

Ser Arg Gly Ala Asn Asn Glu Ser Lys Ala Leu Lys Phe Asp Gly Lys 130 135 140

Val 145	Pro ·	Gly	Glu	Phe	Gln 150		Glu	Val		Gln 155	Ser	Arg	Asp	Asn	Ser 160
Arg	Leu.	Arg	Ser	Gln 165	Ser	Arg	Ser	Arg	Ser 170	Arg	Asn	Arg	Ser	Gln 175	Ser
Arg	Gly	Arg	Gln 180	Gln	Ser	Asn	Asn	Lys 185	Lys	Asp	Asp	Ser	Val 190	Glu	Gln
Ala	Val	Leu 195	Ala	Ala	Leu	Lys	Lys 200	Leu	Gly	Val	Tyr	Thr 205	Gļu	Lys	Gln
Gln	Gln 210	Arg	Ser	Arg	Ser	Lys <sup>.</sup> 215	Ser	Lys	Glu	Arg	Ser 220	Asn	Ser	Lys	Ile
Arg 225	Asp	Thr	Thŗ	Pro	Lys 230	Asn	Glu	Asn	Lys	His 235	Thr	Trp	Lys	Arg	Thr 240
Ala	Gly	ГЛЗ	Gly	Asp 245	Val	Thr	Arg	Phe	Tyr 250	СŢĀ	Thr	Arg	Ser	Asn 255	Ser
Ala	Asn		Gly 260		Ser	Asp	Leu	Val 265	Ala	Asn	Gly	Ser	Ser .270	Ala	Lys
His		Pro 275	ĊŢ	Leu	Ala	Glu	Су <i>s</i> 280	Val	Pro	Ser	Val	Ser 285	Ser	Ile	Leu
Phe	Gly 290	Ser	Tyr	Trp	Thr	Ser 295	Lys	.Glu	Asp	Gly	Asp 300	Gln	Ile	Glu	Val
Thr 305	Phe	Thr	His	Lys	Tyr 310	His	Leu	Pro	Lys	Asp 315	Asp	Pro	Lys	Thr	Gly 320
Gln	Phe	Leu	Gln	Gln 325		Asn	Ala	Tyr	'Ala 330	Arg	Pro	Ser	Glu	Val 335	Ala
Lys	Glu	Gln	Arg 340		Arg	Lys	Ser	Arg 345	Ser	Lys	Ser	Ala	Glu 350	Arg	Ser
Glu	Gln	Glu 355		Val	Pro	Asp	Ala 360	Leu	Ile	Glu	Asn	Tyr 365		Asp	Val
Phe	Asp 370		Thr	Gln	Val	Glu 375		Ile	Asp	Glu	Val 380		Asn		

Ç	2	1	0	>	4	8

<211> 389

<212> PRT

<213> Human coronavirus 229E

<400> 48

Met Ala Thr Val Lys Trp Ala Asp Ala Ser Glu Pro Gln Arg Gly Arg

1 10 | 15

Gln Gly Arg Ile Pro Tyr Ser Leu Tyr Ser Pro Leu Leu Val Asp Ser 20 25 30

Glu Gln Pro Trp Lys Val Ile Pro Arg Asn Leu Val Pro Ile Asn Lys 35 40 45

Lys Asp Lys Asn Lys Leu Ile Gly Tyr Trp Asn Val Gln Lys Arg Phe 50 55 60

Arg Thr Arg Lys Gly Lys Arg Val Asp Leu Ser Pro Lys Leu His Phe 65 70 75 80

Tyr Tyr Leu Gly Thr Gly Pro His Lys Asp Ala Lys Phe Arg Glu Arg 85 90 95

Val Giu Gly Val Val Trp Val Ala Val Asp Gly Ala Lys Thr Glu Pro 100 105 110

Thr Gly Tyr Gly Val Arg Arg Lys Asn Ser Glu Pro Glu Ile Pro His 115 120 125

Phe Asn Gln Lys Leu Pro Asn Gly Val Thr Val Val Glu Glu Pro Asp 130 135 140

Ser Arg Ala Pro Ser Arg Ser Gln Ser Arg Ser Gln Ser Arg Gly Arg
145 150 155 160

Gly Glu Ser Lys Pro Gln Ser Arg Asn Pro Ser Ser Asp Arg Asn His
165 170 175

Asn Ser Gln Asp Asp Ile Met Lys Ala Val Ala Ala Ala Leu Lys Ser 180 185 190

Leu Gly Phe Asp Lys Pro Gln Glu Lys Asp Lys Lys Ser Ala Lys Thr 195 200 205

Gly Thr Pro Lys Pro Ser Arg Asn Gln Ser Pro Ala Ser Ser Gln Thr 210 215 220 Ser Ala Lys Ser Leu Ala Arg Ser Gln Ser Ser Glu Thr Lys Glu Gln 225 230 235 240

Lys His Glu Met Gln Lys Pro Arg Trp Lys Arg Gln Pro Asn Asp Asp 250 255

Val Thr Ser Asn Val Thr Gln Cys Phe Gly Pro Arg Asp Leu Asp His 260 265 270

Asn Phe Gly Ser Ala Gly Val Val Ala Asn Gly Val Lys Ala Lys Gly 275 280 285

Tyr Pro Gln Phe Ala Glu Leu Val Pro Ser Thr Ala Ala Met Leu Phe 290 295 300

Asp Ser His Ile Val Ser Lys Glu Ser Gly Asn Thr Val Val Leu Thr 305 310 315 320

Phe Thr Thr Arg Val Thr Val Pro Lys Asp His Pro His Leu Gly Lys 325 330 335

Phe Leu Glu Glu Leu Asn Ala Phe Thr Arg Glu Met Gln Gln His Pro 340 345 350

Leu Leu Asn Pro Ser Ala Leu Glu Phe Asn Pro Ser Gln Thr Ser Pro 355 360 365

Ala Thr Ala Glu Pro Val Arg Asp Glu Val Ser Ile Glu Thr Asp Ile 370 380

Ile Asp Glu Val Asn 385

<210> 49

<211> 448

<212> PRT

<213> Human coronavirus

<400> 49

Met Ser Phe Thr Pro Gly Lys Gln Ser Ser Ser Arg Ala Ser Ser Gly 1 5. 10 15

Asn Arg Ser Gly Asn Gly Ile Leu Lys Trp Ala Asp Gln Ser Asp Gln 20 25 30

Val Arg Asn Val Gln Thr Arg Gly Arg Arg Ala Gln Pro Lys Gln Thr
35 40 45

- Ala Thr Ser Gln Gln Pro Ser Gly Gly Asn Val Val Pro Tyr Tyr Ser 50 55
- Val Glu Gly Gln Gly Pro Pro Ile Ala Pro Gly Val Pro Ala Thr Glu 85 90 95
- Ala Lys Gly Tyr Trp Tyr Arg His Asn Arg Gly Ser Phe Lys Thr Ala 100 105 110
- Asp Gly Asn Gln Arg Gln Leu Leu Pro Arg Trp Tyr Phe Tyr Tyr Leu 115 120 125
- Gly Thr Gly Pro His Ala Lys Asp Gln Tyr Gly Thr Asp Ile Asp Gly 130 135 140
- Val Tyr Trp Val Ala Ser Asn Gln Ala Asp Val Asn Thr Pro Ala Asp 145 150 155 160
- Ile Val Asp Arg Asp Pro Ser Ser Asp Glu Ala Ile Pro Thr Arg Phe 165 170 175
- Pro Pro Gly Thr Val Leu Pro Gln Gly Tyr Tyr Ile Glu Gly Ser Gly
  180 185 190
- Arg Ser Ala Pro Asn Ser Arg Ser Thr Ser Arg Thr Ser Ser Arg Ala
  195 200 205
- Ser Ser Ala Gly Ser Arg Ser Arg Ala Asn Ser Gly Asn Arg Thr Pro 210 215 220
- Thr Ser Gly Val Thr Pro Asp Met Ala Asp Gln Ile Ala Ser Leu Val. 225 230 240
- Leu Ala Lys Leu Gly Lys Asp Ala Thr Lys Pro Gln Gln Val Thr Lys 245 250 255
- His Thr Ala Lys Glu Val Arg Gln Lys Ile Leu Asn Lys Pro Arg Gln 260 265 270
- Lys Arg Ser Pro Asn Lys Gln Cys Thr Val Gln Gln Cys Phe Gly Lys

WO 2004/096842

275

280

285

Arg Gly Pro Asn Gln Asn Phe Gly Gly Glu Met Leu Lys Leu Gly 290 295 300

Thr Ser Asp Pro Gln Phe Pro Ile Leu Ala Glu Leu Ala Pro Thr Ala 305 310 315 320

Gly Ala Phe Phe Gly Ser Arg Leu Glu Leu Ala Lys Val Gln Asn 325 330 335

Leu Ser Gly Asn Pro Asp Glu Pro Gln Lys Asp Val Tyr Glu Leu Arg 340 345 350

Tyr Asn Gly Ala Ile Arg Phe Asp Ser Thr Leu Ser Gly Phe Glu Thr 355 360 365

Ile Met Lys Val Leu Asn Glu Asn Leu Asn Ala Tyr Gln Gln Gln Asp 370 375 380

Gly Met Met Asn Met Ser Pro Lys Pro Gln Arg Gln Arg Gly His Lys 385 390 395 400

Asn Gly Gln Gly Glu Asn Asp Asn Ile Ser Val Ala Val Pro Lys Ser 405 410 415

Arg Val Gln Gln Asn Lys Ser Arg Glu Leu Thr Ala Glu Asp Ile Ser 420 425 430

Leu Leu Lys Lys Met Asp Glu Pro Tyr Thr Glu Asp Thr Ser Glu Ile 435 440 445

<210> 50 ·

<211> 449

<212> PRT

<213> porcine hemagglutinating encephalomyelitis

<400> 50

Met Ser Phe Thr Pro Gly Lys Gln Ser Ser Ser Arg Ala Ser Ser Gly 1 5 ' 10 15

Asn Arg Ser Gly Asn Gly Ile Leu Lys Trp Ala Asp Gln Ser Asp Gln 20 25 30

Ser Arg Asn Val Gln Thr Arg Gly Arg Arg Val Gln Ser Lys Gln Thr 35 40 45

Ala Thr Ser Gln Gln Pro Ser Gly Gly Thr Val Val Pro Tyr Tyr Ser 50 55 60

- Trp Phe Ser Gly Ile Thr Gln Phe Gln Lys Gly Lys Glu Phe Glu Phe 65 70 75 80
- Ala Glu Gly Gln Gly Val Pro Ile Ala Pro Gly Val Pro Ser Thr Glu 85 90 95
- Ala Lys Gly Tyr Trp Tyr Arg His Asn Arg Arg Ser Phe Lys Thr Ala 100 105 110
- Asp Gly Asn Gln Arg Gln Leu Leu Pro Arg Trp Tyr Phe Tyr Tyr Leu 115 120 125
- Gly Thr Gly Pro His Ala Lys Asp Gln Tyr Gly Thr Asp Ile Asp Gly
  130 135 140
- Val Phe Trp Val Ala Ser Asn Gln Ala Asp Ile Asn Thr Pro Ala Asp 145 150 155 160
- Ile Val Asp Arg Asp Pro Ser Ser Asp Glu Ala Ile Pro Thr Arg Phe
  165 170 175
- Pro Pro Gly Thr Val Leu Pro Gln Gly Tyr Tyr Ile Glu Gly Ser Gly 180 185 190
- Arg Ser Ala Pro Asn Ser Arg Ser Thr Ser Arg Ala Pro Asn Arg Ala 195 200 205
- Pro Ser Ala Gly Ser Arg Ser Arg Ala Asn Ser Gly Asn Arg Thr Ser 210 215 220
- Thr Pro Gly Val Thr Pro Asp Met Ala Asp Gln Ile Ala Ser Leu Val 225 230 235 240
- Leu Ala Lys Leu Gly Lys Asp Ala Thr Lys Pro Gln Gln Val Thr Lys
  245 250 255
- Gln Thr Ala Lys Glu Val Arg Gln Lys Ile Leu Asn Lys Pro Arg Gln 260 270
- Lys Arg Ser Pro Asn Lys Gln Cys Thr Val Gln Gln Cys Phe Gly Lys 275 280 285

Arg Gly Pro Asn Gln Asn Phe Gly Gly Glu Met Leu Lys Leu Gly 290 295 300

Thr Ser Asp Pro Gln Phe Pro Ile Leu Ala Glu Leu Ala Pro Thr Ala 305 310 315 320

Gly Ala Phe Phe Gly Ser Arg Leu Glu Leu Ala Lys Val Gln Asn 325 330 335

114

Leu Ser Gly Asn Pro Asp Glu Pro Gln Lys Asp Val Tyr Glu Leu Arg 340 345 350

Tyr Asn Gly Ala Ile Arg Phe Asp Ser Thr Leu Ser Gly Phe Glu Thr 355 360 365

Ile Met Lys Val Leu Asn Gln Asn Leu Asn Ala Tyr Gln His Gln Glu 370 375 380

Asp Gly Met Met Asn Ile Ser Pro Lys Pro Gln Arg Gln Arg Gly Gln 385 390 395 400

Lys Asn Gly Gln Val Glu Asn Asp Asn Val Ser Val Ala Ala Pro Lys
405 410 415

Ser Arg Val Gln Gln Asn Lys Ser Arg Glu Leu Thr Ala Glu Asp Ile 420 425 430

Ser Leu Leu Lys Lys Met Asp Glu Pro Tyr Thr Glu Asp Thr Ser Glu 435 440 445

Ile

<210> 51

<211> 409

<212> PRT

<213> turkey coronavirus

<400> 51

Met Ala Ser Gly Lys Ala Thr Gly Lys Thr Asp Ala Pro Ala Pro Ile 1 5. 10 15

Ile Lys Leu Gly Gly Pro Lys Pro Pro Lys Val Gly Ser Ser Gly Asn 20 25 30

Ala Ser Trp Phe Gln Ser Ile Lys Ala Lys Lys Leu Asn Ser Pro Gln 35 40 , 45

Pro Lys Phe Glu Gly Ser Gly Val Pro Asp Asn Glu Asn Ile Lys Thr 50 55 60

- Ser Gln Gln His Gly Tyr Trp Arg Arg Gln Ala Arg Phe Lys Pro Gly 65 70 75 80
- Lys Gly Gly Arg Lys Pro Val Pro Asp Ala Trp Tyr Phe Tyr Tyr Thr 85 90 95
- Gly Thr Gly Pro Ala Ala Asp Leu Asn Trp Gly Asp Thr Gln Asp Gly
  100 105 110
- Ile Val Trp Val Ala Ala Lys Gly Ala Asp Val Lys Ser Arg Ser Asn 115 120 125
- Gln Gly Thr Arg Asp Pro Asp Lys Phe Asp Gln Tyr Pro Leu Arg Phe 130 135 140
- Ser Asp Gly Gly Pro Asp Ser Asn Phe Arg Trp Asp Phe Ile Pro Leu 145 150 155 160
- His Arg Gly Arg Ser Gly Arg Ser Thr Ala Ala Ser Ser Ala Ala Ser 165 170 175
- Ser Arg Ala Pro Ser Arg Asp Gly Ser Arg Gly Arg Arg Ser Gly Ser 180 185 190
- Glu Asp Asp Leu Ile Ala Arg Ala Ala Lys Ile Ile Gln Asp Gln Gln 195 200 205
- Lys Lys Gly Ser Arg Ile Thr Lys Ala Lys Ala Asp Glu Met Ala His 210 215 220
- Val Phe Gly Pro Arg Thr Lys Gly Lys Glu Gly Asn Phe Gly Asp Asp 245 250 255
- Lys Met Asn Glu Glu Gly Ile Lys Asp Gly Arg Val Thr Ala Met Leu 260 265 270
- Asn Leu Val Pro Ser Ser His Ala Cys Leu Phe Gly Ser Arg Val Thr 275 280 285

Pro Lys Leu Gln Pro Asp Gly Leu His Leu Arg Phe Glu Phe Thr Thr 290 295 Val Val Pro Arg Asp Asp Pro Gln Phe Asp Asn Tyr Val Thr Ile Cys 310 315 320 Asp Gln Cys Val Asp Gly Ile Gly Thr Arg Pro Lys Asp Asn Glu Pro 325 330 335 Arg Pro Lys Ser Arg Pro Ser Ser Arg Pro Ala Thr Arg Gly Asn Ser 340 345 350 Pro Ala Pro Arg Gln Gln Arg Pro Lys Lys Glu Lys Lys Pro Lys Lys 360 365 Gln Asp Asp Glu Val Asp Lys Ala Leu Thr Ser Asp Glu Glu Arg Asn 375 380 Asn Ala Gln Leu Glu Phe Asp Asp Glu Pro Lys Val Ile Asn Trp Gly 385 390 395 400. Asp Ser Ala Leu Gly Glu Asn His Leu 405 <210> 52 <211> 1173 <212> PRT <213> Human coronavirus 229E <400> 52 Met Phe Val Leu Leu Val Ala Tyr Ala Leu Leu His Ile Ala Gly Cys 1 5 10 15 Gln Thr Thr Asn Gly Leu Asn Thr Ser Tyr Ser Val Cys Asn Gly Cys Val Gly Tyr Ser Glu Asn Val Phe Ala Val Glu Ser Gly Gly Tyr Ile 35 Pro Ser Asp Phe Ala Phe Asn Asn Trp Phe Leu Leu Thr Asn Thr Ser Ser Val Val Asp Gly Val Val Arg Ser Phe Gln Pro Leu Leu Leu Asn

Cys Leu Trp Ser Val Ser Gly Leu Arg Phe Thr Thr Gly Phe Val Tyr

165

95

			•			•				- •			•			
	Phe	Asn		Thr 100		Arg	Gly		Cys 105		Gly	Phe	Ser	Ser 110	Asp	Val
•	Leu	Ser	Asp 115	Val	Ile	Arg	Tyr	Asn 120	Leu	Asn	Phe	Glu	Glu 125	Asn	Leu	Arg
	Arg	Gly 130	Thr	lle	Leu	Phe	Lys 135	Thr	Ser	Tyr		Val 140		Val	Phe	Tyr
	Cvs	Thr	Asn	Asn	Thr	Leu	Val	Sec	Glv	Asp	Δla	His	Tle	Pro	Phe	Glv

Thr Val Leu Gly Asn Phe Tyr Cys Phe Val Asn Thr Thr Ile Gly Thr

155

170

Glu Thr Thr Ser Ala Phe Val Gly Ala Leu Pro Lys Thr Val Arg Glu 180 185 190

Phe Val Ile Ser Arg Thr Gly His Phe Tyr Ile Asn Gly Tyr Arg Tyr 195 200 205

Phe Thr Leu Gly Asn Val Glu Ala Val Asn Phe Asn Val Thr Thr Ala 210 215 220

Glu Thr Thr Asp Phe Phe Thr Val Ala Leu Ala Ser Tyr Ala Asp Val 225 230 235 240

Leu Val Asn Val Ser Gln Thr Ser Ile Ala Asn Ile Ile Tyr Cys Asn 245 250 255

Ser Val Ile Asn Arg Leu Arg Cys Asp Gln Leu Ser Phe Tyr Val Pro 260 265 270

Asp Gly Phe Tyr Ser Thr Ser Pro Ile Gln Ser Val Glu Leu Pro Val 275 280 285

Ser Ile Val Ser Leu Pro Val Tyr His Lys His Met Phe Ile Val Leu 290 295 300

Tyr Val Asp Phe Lys Pro Gln Ser Gly Gly Gly Lys Cys Phe Asn Cys 305 310 315 320

Tyr Pro Ala Gly Val Asn Ile Thr Leu Ala Asn Phe Asn Glu Thr Lys 325 330 335 Gly Pro Leu Cys Val Asp Thr Ser His Phe Thr Thr Lys Tyr Val Ala 340 345 350

- Val Tyr Ala Asn Val Gly Arg Trp Ser Ala Ser Ile Asn Thr Gly Asn 355 360 365
- Cys Pro Phe Ser Phe Gly Lys Val Asn Asn Phe Val Lys Phe Gly Ser 370 380
- Val Cys Phe Ser Leu Lys Asp Ile Pro Gly Gly Cys Ala Met Pro Ile 385 . 390 395 400
- Val Ala Asn Trp Ala Tyr Ser Lys Tyr Tyr Thr Ile Gly Thr Leu Tyr
  405 410 415
- Val Ser Trp Ser Asp Gly Asp Gly Ile Thr Gly Val Pro Gln Pro Val 420 425 430
- Glu Gly Val Ser Ser Phe Met Asn Val Thr Leu Asp Lys Cys Thr Lys.
  435
  440
  445
- Tyr Asn Ile Tyr Asp Val Ser Gly Val Gly Val Ile Arg Val Ser Asn 450 455 460
- Asp Thr Phe Leu Asn Gly Ile Thr Tyr Thr Ser Thr Ser Gly Asn Leu 465 470 475 480
- Leu Gly Phe Lys Asp Val Thr Lys Gly Thr Ile Tyr Ser Ile Thr Pro 485 490 495 .
- Cys Asn Pro Pro Asp Gln Leu Val Val Tyr Gln Gln Ala Val Val Gly 500 505 510
- Ala Met Leu Ser Glu Asn Phe Thr Ser Tyr Gly Phe Ser Asn Val Val 515 520 525
- Glu Leu Pro Lys Phe Phe Tyr Ala Ser Asn Gly Thr Tyr Asn Cys Thr 530 535 540
- Asp Ala Val Leu Thr Tyr Ser Ser Phe Gly Val Cys Ala Asp Gly Ser 545 550 555 560
- Ile Ile Ala Val Gln Pro Arg Asn Val Ser Tyr Asp Ser Val Ser Ala 565 570 575

Ile Val Thr Ala Asn Leu Ser Ile Pro Ser Asn Trp Thr Ile Ser Val 580 585 590

- Gln Val Glu Tyr Leu Gln Ile Thr Ser Thr Pro Ile Val Val Asp Cys
  595 600 605
- Ser Thr Tyr Val Cys Asn Gly Asn Val Arg Cys Val Glu Leu Leu Lys 610 620
- Gin Tyr Thr Ser Ala Cys Lys Thr Ile Glu Asp Ala Leu Arg Asn Ser 625 630 635 635
- Ala Arg Leu Glu Ser Ala Asp Val Ser Glu Met Leu Thr Phe Asp Lys 645 650 655
- Lys Ala Phe Thr Leu Ala Asn Val Ser Ser Phe Gly Asp Tyr Asn Leu 660 665 670
- Ser Ser Val Ile Pro Ser Leu Pro Thr Ser Gly Ser Arg Val Ala Gly 675 680 685
- Arg Ser Ala Ile Glu Asp Ile Leu Phe Ser Lys Ile Val Thr Ser Gly 690 695 700
- Leu Gly Thr Val Asp Ala Asp Tyr Lys Asn Cys Thr Lys Gly Leu Ser 705 710 715 720
- Ile Ala Asp Leu Ala Cys Ala Gln Tyr Tyr Asn Gly Ile Met Val Leu 725 730 735
- Pro Gly Val Ala Asp Ala Glu Arg Met Ala Met Tyr Thr Gly Ser Leu 740 745 750
- Ile Gly Gly Ile Ala Leu Gly Gly Leu Thr Ser Ala Val Ser Ile Pro
  755 760 765
- Phe Ser Leu Ala Ile Gln Ala Arg Leu Asn Tyr Val Ala Leu Gln Thr 770 780
- Asp Val Leu Gln Glu Asn Gln Lys Ile Leu Ala Ala Ser Phe Asn Lys 785 790 795 800
- Ala Met Thr Asn Ile Val Asp Ala Phe Thr Gly Val Asn Asp Ala Ile 805 810 815

Thr Gln Thr Ser Gln Ala Leu Gln Thr Val Ala Thr Ala Leu Asn Lys 820 825 830

Ile Gln Asp Val Val Asn Gln Gln Gly Asn Ser Leu Asn His Leu Thr 835 840 845

1077

- Ser Gln Leu Arg Gln Asn Phe Gln Ala Ile Ser Ser Ser Ile Gln Ala 850 855 860
- Ile Tyr Asp Arg Leu Asp Thr Ile Gln Ala Asp Gln Gln Val Asp Arg 865 870 875 880
- Leu Ile Thr Gly Arg Leu Ala Ala Leu Asn Val Phe Val Ser His Thr 885 890 895
- Leu Thr Lys Tyr Thr Glu Val Arg Ala Ser Arg Gln Leu Ala Gln Gln 900 905 910
- Lys Val Asn Glu Cys Val Lys Ser Gln Ser Lys Arg Tyr Gly Phe Cys 915 920 925
- Gly Asn Gly Thr His Ile Phe Ser Ile Val Asn Ala Ala Pro Glu Gly 930 935 940
- Leu Val Phe Leu His Thr Val Leu Leu Pro Thr Gln Tyr Lys Asp Val 945 950 955 960
- Glu Ala Trp Ser Gly Leu Cys Val Asp Gly Thr Asn Gly Tyr Val Leu 965 970 975
- Arg Gln Pro Asn Leu Ala Leu Tyr Lys Glu Gly Asn Tyr Tyr Arg Ile 980 985 990
- Thr Ser Arg Ile Met Phe Glu Pro Arg Ile Pro Thr Met Ala Asp Phe 995 1000 1005
- Val Gln Ile Glu Asn Cys Asn Val Thr Phe Val Asn Ile Ser Arg 1010 1015 1020
- Ser Glu Leu Gln Thr Ile Val Pro Glu Tyr Ile Asp Val Asn Lys 1025 1030 1035
- Thr Leu Gln Glu Leu Ser Tyr Lys Leu Pro Asn Tyr Thr Val Pro 1040 1045 1050
- Asp Leu Val Val Glu Gln Tyr Asn Gln Thr Ile Leu Asn Leu Thr

1060

1065

Ser Glu Ile Ser Thr Leu Glu Asn Lys Ser Ala Glu Leu Asn Tyr . 1070 1075 1080

Thr Val Gln Lys Leu Gln Thr Leu Ile Asp Asn Ile Asn Ser Thr 1085 1090 1095

Leu Val Asp Leu Lys Trp Leu Asn Arg Val Glu Thr Tyr Ile Lys
1100 1105 1110

Trp. Pro Trp Trp Val Trp Leu Cys Ile Ser Val Val Leu Ile Phe 1115 1120 1125

Val Val Ser Met Leu Leu Cys Cys Cys Ser Thr Gly Cys Cys 1130 1135 1140

Gly Phe Phe Ser Cys Phe Ala Ser Ser Ile Arg Gly Cys Cys Glu 1145 1150 1155

Ser Thr Lys Leu Pro Tyr Tyr Asp Val Glu Lys Ile His Ile Gln 1160 1165 1170

<2103 53

<211> 1164

<212> PRT

<213> Avian infectious bronchitis virus

<400> 53

Met Leu Gly Lys Ser Leu Phe Leu Val Thr Ile Leu Cys Ala Leu Cys 1 5 10 15

Ser Ala Asn Leu Phe Asp Pro Ala Asn Tyr Val Tyr Tyr Gln Ser 20 25 30

Ala Phe Arg Pro Ser Asn Gly Trp His Leu Gln Gly Gly Ala Tyr Ala 35 40 45

Val Val Asn Ser Ser Asn Tyr Ala Asn Asn Ala Gly Ser Ala Ser Glu 50 55 60

Cys Thr Val Gly Val Ile Lys Asp Val Tyr Asn Gln Ser Ala Ala Ser 65 70 75 80

Ile Ala Met Thr Ala Pro Leu Gln Gly Met Ala Trp Ser Lys Ser Gln 85 90 95

WO 2004/096842 PCT/CA2004/000626

Phe Cys Ser Ala His Cys Asp Phe Ser Glu Ile Thr Val Phe Val Thr 100 105 110 His Cys Tyr Ser Ser Gly Ser Gly Ser Cys Pro Ile Thr Gly Met Ile 115 120 125 Ala Arg Gly His Ile Arg Ile Ser Ala Met Lys Asn Gly Ser Leu Phe 135 140 Tyr Asn Leu Thr Val Ser Val Ser Lys Tyr Pro Asn Phe Lys Ser Phe 145 150 155 160 Gln Cys Val Asn Asn Phe Thr Ser Val Tyr Leu Asn Gly Asp Leu Val 165 170 175 Phe Thr Ser Asn Lys Thr Thr Asp Val Thr Ser Ala Gly Val Tyr Phe 185 190 Lys Ala Gly Gly Pro Val Asn Tyr Ser Ile Met Lys Glu Phe Lys Vai 200 Leu Ala Tyr Phe Val Asn Gly Thr Ala Gln Asp Val Ile Leu Cys Asp 210 215 220 Asn Ser Pro Lys Gly Leu Leu Ala Cys Gln Tyr Asn Thr Gly Asn Phe 225 230 235 Ser Asp Gly Phe Tyr Pro Phe Thr Asn Ser Thr Leu Val Arg Glu Lys 245 250 Phe Ile Val Tyr Arg Glu Ser Ser Val Asn Thr Thr Leu Ala Leu Thr Asn Phe Thr Phe Thr Asn Val Ser Asn Ala Gln Pro Asn Ser Gly Gly 275 . 280 Val His Thr Phe His Leu Tyr Gln Thr Gln Thr Ala Gln Ser Gly Tyr . 295 .300 Tyr Asn Phe Asn Leu Ser Phe Leu Ser Gln Phe Val Tyr Lys Ala Ser Asp Tyr Met Tyr Gly Ser Tyr His Pro Ile Cys Ala Phe Arg Pro Glu 325

Thr Ile Asn Ser Gly Leu Trp Phe Asn Ser Leu Ser Val Ser Leu Thr 340 345 350

- Tyr Gly Pro Leu Gln Gly Gly Tyr Lys Gln Ser Val Phe Ser Gly Lys 355 360 365
- Ala Thr Cys Cys Tyr Ala Tyr Ser Tyr Asn Gly Pro Arg Ala Cys Lys 370 375 380
- Gly Val Tyr Ser Gly Glu Leu Ser Arg Asp Phe Glu Cys Gly Leu Leu 385 390 395 400
- Val Tyr Val Thr Lys Ser Asp Gly Ser Arg Ile Gln Thr Arg Thr Glu 405 410 415
- Pro Leu Val Leu Thr Gln His Asn Tyr Asn Asn Ile Thr Leu Asp Lys 420 425 430
- Cys Val Ala Tyr Asn Ile Tyr Gly Arg Val Gly Gln Gly Phe Ile Thr 435 440 445
- Asn Val Thr Asp Ser Val Ala Asn Phe Ser Tyr Leu Ala Asp Gly Gly 450 455 460
- Leu Ala Ile Leu Asp Thr Ser Gly Ala Ile Asp Val Phe Val Val Gln 465 470 475 480
- Gly Ser Tyr Gly Leu Asn Tyr Tyr Lys Val Asn Pro Cys Glu Asp Val 485 490 495
- Asn Gln Gln Phe Val Val Ser Gly Gly Asn Ile Val Gly Ile Leu Thr 500 505 510
- Ser Arg Asn Glu Thr Gly Ser Glu Gln Val Glu Asn Gln Phe Tyr Val 515 520 525
- Lys Leu Thr Asn Ser Ser His Arg Arg Arg Arg Ser Ile Gly Gln Asn 530 540
- Val Thr Ser Cys Pro Tyr Val Ser Tyr Gly Arg Phe Cys Ile Glu Pro 545 550 555 560
- Asp Gly Ser Leu Lys Met Ile Val Pro Glu Glu Leu Lys Gln Phe Val 565 570 575
- Ala Pro Leu Leu Asn Ile Thr Glu Ser Val Leu Ile Pro Asn Ser Phe

585

590

Asn Leu Thr Val Thr Asp Glu Tyr Ile Gln Thr Arg Met Asp Lys Val 595 600 605

Gln Ile Asn Cys Leu Gln Tyr Val Cys Gly Asn Ser Leu Glu Cys Arg 610 615 620

Lys Leu Phe Gln Gln Tyr Gly Pro Val Cys Asp Asn Ile Leu Ser Val 625 630 635 640

Val Asn Ser Val Ser Gln Lys Glu Asp Met Glu Leu Leu Ser Phe Tyr 645 650 655

Ser Ser Thr Lys Pro Lys Gly Tyr Asp Thr Pro Val Leu Ser Asn Val 660 665 670

Ser Thr Gly Glu Phe Asn Ile Ser Leu Leu Thr Pro Pro Ser Ser 675 680 685

Pro Ser Gly Arg Ser Phe Val Glu Asp Leu Leu Phe Thr Ser Val Glu 690 695 700

Thr Val Gly Leu Pro Thr Asp Ala Glu Tyr Lys Lys Cys Thr Ala Gly 705 710 715 720

.

Pro Leu Gly Thr Leu Lys Asp Leu Ile Cys Ala Arg Glu Tyr Asn Gly 725 730 735

Leu Val Leu Pro Pro Ile Ile Thr Ala Asp Met Gln Thr Met Tyr 740 745 750

Thr Ala Ser Leu Val Gly Ala Met Ala Phe Gly Gly Ile Thr Ser Ala 755 760 765

Ala Ala Ile Pro Phe Ala Thr Gln Ile Gln Ala Arg Ile Asn His Leu 770 775 780

Gly Ile Ala Gln Ser Leu Leu Met Lys Asn Gln Glu Lys Ile Ala Ala 785 790 795 800

Ser Phe Asn Lys Ala Ile Gly His Met Gln Glu Gly Phe Arg Ser Thr 805 810 815

Ser Leu Ala Leu Gln Gln Val Gln Asp Val Val Asn Lys Gln Ser Ala 820 825 830 Ile Leu Thr Glu Thr Met Asn Ser Leu Asn Lys Asn Phe Gly Ala Ile 835 840 845

- Ser Ser Val Ile Gin Asp Ile Tyr Ala Gin Leu Asp Ala Ile Gin Ala 850 855 860
- Asp Ala Gln Val Asp Arg Leu Ile Thr Gly Arg Leu Ser Ser Leu Ser 865 870 875 880
- Val Leu Ala Ser Ala Lys Gln Ser Glu Tyr Ile Arg Val Ser Gln Gln 885 890 895
- Arg Glu Leu Ala Thr Gln Lys Ile Asn Glu Cys Val Lys Ser Gln Ser 900 905 910
- Asn Arg Tyr Gly Phe Cys Gly Ser Gly Arg His Val Leu Ser Ile Pro 915 920 925
- Gln Asn Ala Pro Asn Gly Ile Val Phe Ile His Phe Thr Tyr Thr Pro 930 935 940
- Glu Thr Phe Val Asn Val Thr Ala Ile Val Gly Phe Cys Val Asn Pro 945 950 955 960
- Leu Asn Ala Ser Gln Tyr Ala Ile Val Pro Ala Asn Gly Arg Gly Ile 965 , 970 975
- Phe Ile Gln Val Asn Gly Thr Tyr Tyr Ile Thr Ser Arg Asp Met Tyr 980 985 990
- Met Pro Arg Asp Ile Thr Ala Gly Asp Ile Val Thr Leu Thr Ser Cys 995 1000 1005
- Gln Ala Asn Tyr Val Asn Val Asn Lys Thr Val Ile Thr Thr Phe 1010 1015 1020
- Val Glu Asp Asp Asp Phe Asn Phe Asp Asp Glu Leu Ser Lys Trp 1025 1030 1035
- Trp Asn Asp Thr Lys His Gly Leu Pro Asp Phe Asp Asp Phe Asn 1040 1045 1050
- Tyr Thr Val Pro Ile Leu Asn Ile Ser Gly Glu Ile Asp Asn Ile 1055 1060 1065

Gln Gly Val Ile Gln Gly Leu Asn Asp Ser Leu Ile Asn Leu Glu 1070 1075 1080

Glu Leu Ser Ile Ile Lys Thr Tyr Ile Lys Trp Pro Trp Tyr Val 1085 . 1090 1095

Trp Leu Ala Ile Gly Phe Ala Ile Ile Ile Phe Ile Leu Ile Leu 1100 1105 1110

Gly Trp Val Phe Phe Met Thr Gly Cys Cys Gly Cys Cys Gly 1115 1120 1125

Cys Phe Gly Ile Ile Pro Leu Ile Ser Lys Cys Gly Lys Lys Ser 1130 1135 1140

Ser Tyr Tyr Thr Thr Phe Asp Asn Asp Val Val Thr Glu Gln Tyr 1145 1150 1155

Arg Pro Lys Lys Ser Val

<210> 54

<211> 1363

<212> PRT

<213> Bovine coronoavirus

<400> 54

Met Phe Leu Ile Leu Leu Ile Ser Leu Pro Met Ala Phe Ala Val Ile 1 5 10 15

Gly Asp Leu Lys Cys Thr Thr Val Ser Ile Asn Asp Val Asp Thr Gly 20 25 30

Ala Pro Ser Ile Ser Thr Asp Ile Val Asp Val Thr Asn Gly Leu Gly 35 40 45

Thr Tyr Tyr Val Leu Asp Arg Val Tyr Leu Asn Thr Thr Leu Leu Leu 50 55 60

Asn Gly Tyr Tyr Pro Thr Ser Gly Ser Thr Tyr Arg Asn Met Ala Leu 65 70 75 80

Lys Gly Thr Leu Leu Ser Arg Leu Trp Phe Lys Pro Pro Phe Leu 85 90 95

Ser Asp Phe Ile Asn Gly Ile Phe Ala Lys Val Lys Asn Thr Lys Val

105

1:10

Ile Lys Lys Gly Val Met Tyr Ser Glu Phe Pro Ala Ile Thr Ile Gly
115 120 125

Ser Thr Phe Val Asn Thr Ser Tyr Ser Val Val Gln Pro His Thr
130 135 140

Thr Asn Leu Asp Asn Lys Leu Gln Gly Leu Leu Glu Ile Ser Val Cys 145 150 155 160

Gln Tyr Thr Met Cys Glu Tyr Pro His Thr Ile Cys His Pro Lys Leu 165 170 175

Gly Asn Lys Arg Val Glu Leu Trp His Trp Asp Thr Gly Val Val Ser 180 185 190

Cys Leu Tyr Lys Arg Asn Phe Thr Tyr Asp Val Asn Ala Asp Tyr Leu 195 200 205

Tyr Phe His Phe Tyr Gln Glu Gly Gly Thr Phe Tyr Ala Tyr Phe Thr 210 215 220

Asp Thr Gly Val Val Thr Lys Phe Leu Phe Asn Val Tyr Leu Gly Thr 225 230 235 240

Val Leu Ser His Tyr Tyr Val Leu Pro Leu Thr Cys Ser Ser Ala Met
245 250 255

Thr Leu Glu Tyr Trp Val Thr Pro Leu Thr Ser Lys Gln Tyr Leu Leu 260 265 270

Ala Phe Asn Gln Asp Gly Val Ile Phe Asn Ala Val Asp Cys Lys Ser 275 280 285

Asp Phe Met Ser Glu Ile Lys Cys Lys Thr Leu Ser Ile Ala Pro Ser 290 295 300

Thr Gly Val Tyr Glu Leu Asn Gly Tyr Thr Val Gln Pro Ile Ala Asp 305 310 315 320

Val Tyr Arg Arg Ile Pro Asn Leu Pro Asp Cys Asn Ile Glu Ala Trp 325 330 335

Leu Asn Asp Lys Ser Val Pro Ser Pro Leu Asn Trp Glu Arg Lys Thr 340 345 350

Phe Ser Asn Cys Asn Phe Asn Met Ser Ser Leu Met Ser Phe Ile Gln 355 360 365 Ala Asp Ser Phe Thr Cys Asn Asn Ile Asp Ala Ala Lys Ile Tyr Gly 370 (1) 375 380 Met Cys Phe Ser Ser Ile Thr Ile Asp Lys Phe Ala Ile Pro Asn Gly 390 395 400 Arg Lys Val Asp Leu Gln Leu Gly Asn Leu Gly Tyr Leu Gln Ser Phe 405 Asn Tyr Arg Ile Asp Thr Thr Ala Thr Ser Cys Gln Leu Tyr Tyr Asn . 425 Leu Pro Ala Ala Asn Val Ser Val Ser Arg Phe Asn Pro Ser Thr Trp 435 440 445 Asn Arg Arg Phe Gly Phe Thr Glu Gln Phe Val Phe Lys Pro Gln Pro 460 450 455 Val Gly Val Phe Thr His His Asp Val Val Tyr Ala Gln His Cys Phe 465 . 470 475 480 Lys Ala Pro Lys Asn Phe Cys Pro Cys Lys Leu Asp Gly Ser Leu Cys 490 495 485. Val Gly Asn Gly Pro Gly Ile Asp Ala Gly Tyr Lys Asn Ser Gly Ile Gly Thr Cys Pro Ala Gly Thr Asn Tyr Leu Thr Cys His Asn Ala Ala 515 520 Gln Cys Asp Cys Leu Cys Thr Pro Asp Pro Ile Thr Ser Lys Ser Thr 530 535 540 Gly Pro Tyr Lys Cys Pro Gln Thr Lys Tyr Leu Val Gly Ile Gly Glu 555 545 His Cys Ser Gly Leu Ala Ile Lys Ser Asp Tyr Cys Gly Gly Asn Pro 570 565 Cys Thr Cys Gln Pro Gln Ala Phe Leu Gly Trp Ser Val Asp Ser Cys

585

Leu Gln Gly Asp Arg Cys Asn Ilé Phe Ala Asn Phe Ile Phe His Asp 595 600 605

- Val Asn Ser Gly Thr Thr Cys Ser Thr Asp Leu Gln Lys Ser Asn Thr 610 615 620
- Asp Ile Ile Leu Gly Val Cys Val Asn Tyr Asp Leu Tyr Gly Ile Thr 625 630 635
- Gly Gln Gly Ile Phe Val Glu Val Asn Ala Thr Tyr Tyr Asn Ser Trp
  645 650 655
- Gln Asn Leu Tyr Asp Ser Asn Gly Asn Leu Tyr Gly Phe Arg Asp 660 665 670
- Tyr Leu Thr Asn Arg Thr Phe Met Ile Arg Ser Cys Tyr Ser Gly Arg 675 680 685
- Val Ser Ala Ala Phe His Ala Asn Ser Ser Glu Pro Ala Leu Leu Phe 690 695 700
- Arg Asn Ile Lys Cys Asn Tyr Val Phe Asn Asn Thr Leu Ser Arg Gln 705 710 715 720
- Leu Gln Pro Ile Asn Tyr Phe Asp Ser Tyr Leu Gly Cys Val Val Asn 725 730 735
- Ala Asp Asn Ser Thr Ser Ser Val Val Gln Thr Cys Asp Leu Thr Val
  740 745 750
- Gly Ser Gly Tyr Cys Val Asp Tyr Ser Thr Lys Arg Arg Ser Arg Arg
  755 760 765
- Ala Ile Thr Thr Gly Tyr Arg Phe Thr Asn Phe Glu Pro Phe Thr Val 770 775 780
- Asn Ser Val Asn Asp Ser Leu Glu Pro Val Gly Gly Leu Tyr Glu Ile 785 790 795 800
- Gln Ile Pro Ser Glu Phe Thr Ile Gly Asn Met Glu Glu Phe Ile Gln 805 810 815
- Thr Ser Ser Pro Lys Val Thr Ile Asp Cys Ser Ala Phe Val Cys Gly 820 825 830

Asp Tyr Ala Ala Cys Lys Ser Gln Leu Val Glu Tyr Gly Ser Phe Cys 835 840 845

- Asp Asn Ile Asn Ala Ile Leu Thr Glu Val Asn Glu Leu Leu Asp Thr 850 860
- Thr Gln Leu Gln Val Ala Asn Ser Leu Met Asn Gly Val Thr Leu Ser 865 870 875 880
- Thr Lys Leu Lys Asp Gly Val Asn Phe Asn Val Asp Asp Ile Asn Phe 885. 890 895
- Ser Pro Val Leu Gly Cys Leu Gly Ser Ala Cys Asn Lys Val Ser Ser 900 905 910
- Arg Ser Ala Ile Glu Asp Leu Leu Phe Ser Lys Val Lys Leu Ser Asp 915 , 920 925
- . Val Gly Phe Val Glu Ala Tyr Asn Asn Cys Thr Gly Gly Ala Glu Ile 930 935 940
  - Arg Asp Leu Ile Cys Val Gln Ser Tyr Asn Gly Ile Lys Val Leu Pro 945 950 960
  - Pro Leu Leu Ser Val Asn Gln Ile Ser Gly Tyr Thr Leu Ala Ala Thr 965 970 975
  - Ser Ala Ser Leu Phe Pro Pro Leu Ser Ala Ala Val Gly Val Pro Phe 980 985 990
  - Tyr Leu Asn Val Gln Tyr Arg Ile Asn Gly Ile Gly Val Thr Met Asp 995 1000 1005
  - Val Leu Ser Gln Asn Gln Lys Leu Ile Ala Asn Ala Phe Asn Asn 1010 1015 1020
  - Ala Leu Asp Ala Ile Gln Glu Gly Phe Asp Ala Thr Asn Ser Ala 1025 1030 1035
  - Leu Val Lys Ile Gln Ala Val Val Asn Ala Asn Ala Glu Ala Leu 1040 1045 1050
  - Asn Asn Leu Leu Gln Gln Leu Ser Asn Arg Phe Gly Ala Ile Ser 1055 1060 1065
  - Ser Ser Leu Gln Glu Ile Leu Ser Arg Leu Asp Ala Leu Glu Ala

WC	2004/	U2U04.	_										. • •	IICA
:	1070		, -	•	· .	1075	•				1080	•		•
Gln	Ala 1085	Gln :	Ile	Asp	Arg	Leu 1090	Île	Asn	Gly	Arg	Leu 1095		Ala	Leu ·
Asn	Vál 1100	Tyr	Val	Ser	Gln	Gln 1105		Ser	Asp		Thr 1110	Leu	Val	Lys.
Phe	Ser 1115		Ala	Gln	·Ala	Met 1120	Glu	Lys	Val	Asn	Glu 1125	Cys	Val	Lys
Ser	Gln 1130	Ser	Ser	Arg	Ile	Asn 1135	Phe	Cys	Gly	Asn	Gly 1140	Asn	His	Ile
Ile	Ser 1145		Val	Gln	Asn	Ala 1150	Pro	Tyr	Gly	Leu	Tyr 1155		Ile	His
Phe	Ser 1160	Tyr	'Val	Pro	Thr	Lys 1165		Val	Thr	Ala	Lys 1170		Ser	Pro
Gly	Leu 1175	Cys	Ile	Ala	Gly	Asp 1180	Arg	Gly	Ile	Ala	Pro 1185	ГÃЗ	Ser	Gly
Tyr	Phe 1190	Val	Asn	Val	Asn	Asn 1195	Thr	Trp	Met	Phe	Thr 1200	Gly	Ser	Gly
Tyr	Tyr 1205	Tyr	Pro	Glu	Pro	Ile 1210		Gly	Asn	Asn	Val 1215	Val	Val	Met
Ser	Thr 1220		Ala	Val	Asn	Tyr 1225		Lys	Ala	Pro	Asp 1230	Val	Met	Leu
	Ile 1235		Thr	Pro	Asn	Leu 1240		Asp	Phe	Lys	Glu 1245		Leu	Asp
Gln	Trp 1250		Lys	Asn	Gln	Thr 1255		Val	Ala	Pro	Asp 1260		Ser	Leu
Asp	Tyr 1265		Asn	Val	Thr	Phe 1270		Asp	Leu	Gln	Asp 1275		Met	Asn
Arg	Leu 1280		Glu	Ala	Ile	Lys 1285		Leu	Asn	Gln	Ser 1290	-	Ile	Asn

Leu Lys Asp Ile Gly Thr Tyr Glu Tyr Tyr Val Lys Trp Pro Trp 1295 1300 1305

Tyr Val Trp Leu Leu Ile Gly Phe Ala Gly Val Ala Met Leu Val 1310 , 1315

Leu Leu Phe Phe Ile Cys Cys Cys Thr Gly Cys Gly Thr Ser Cys 1325 1330 1335

Phe Lys Ile Cys Gly Gly Cys Cys Asp Asp Tyr Thr Gly His Gln 1340 1345

Glu Leu Val Ile Lys Thr Ser His Asp Asp · 1355 1360

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<212> PRT

<213> canine coronavirus

<400> 55

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Ile Cys Thr Ser Asn Asn Asp Cys Val Gln Gly Asn Val Thr Gln Leu 20 25 30

Pro Gly Asn Glu Asn Ile Ile Lys Asp Phe Leu Phe His Thr Phe Lys 40

Glu Glu Pro Ser Val Val Gly Gly Tyr Tyr Pro Thr Glu Val Trp 55

Tyr Asn Cys Ser Arg Ser Ala Thr Thr Thr Ala Tyr Lys Asp Phe Ser . 70

Asn Ile His Ala Phe Tyr Phe Asp Met Glu Ala Met Glu Asn Ser Thr 85 90

Gly Asn Ala Arg Gly Lys Pro Leu Leu Val His Val His Gly Asp Pro 105

Val Ser Ile Ile Ile Tyr Ile Ser Ala Tyr Arg Asp Asp Val Gln Pro 115 120

Arg Pro Leu Lys His Gly Leu Leu Cys Ile Thr Lys Asn Lys Ile 130 135

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Ile Asp Tyr Asn Thr Phe Thr Ser Ala Gln Trp Ser Ala Ile Cys Leu 155 160 150 Gly Asp Asp Arg Lys Ile Pro Phe Ser Val Ile Pro Thr Asp Asn Gly 165 170 Thr Lys Ile Phe Gly Leu Glu Trp Asn Asp Asp Tyr Val Thr Ala Tyr 180 185 Ile Ser Asp Arg Ser His His Leu Asn Ile Asn Asn Asn Trp Phe Asn 195 200 205 Asn Val Thr Ile Leu Tyr Ser Arg Ser Ser Ser Ala Thr Trp Gln Lys 210 215 220 Ser Ala Ala Tyr Val Tyr Gln Gly Val Ser Asn Phe Thr Tyr Tyr Lys 230 235 240 Leu Asn Asn Thr Asn Gly Leu Lys Ser Tyr Glu Leu Cys Glu Asp Tyr 250 255 245 Glu Tyr Cys Thr Gly Tyr Ala Thr Asn Val Phe Ala Pro Thr Val Gly 260 265 270 Gly Tyr Ile Pro His Gly Phe Ser Phe Asn Asn Trp Phe Met Arg Thr 275 280 285 Asn Ser Ser Thr Phe Val Ser Gly Arg Phe Val Thr Asn Gln Pro Leu 295 Leu Val Asn Cys Leu Trp Pro Val Pro Ser Phe Gly Val Ala Ala Gln 305 310 Gln Phe Cys Phe Glu Gly Ala Gln Phe Ser Gln Cys Asn Gly Val Ser . 330 325 335 Leu Asn Asn Thr Val Asp Val Ile Arg Phe Asn Leu Asn Phe Thr Ala Leu Val Gln Ser Gly Met Gly Ala Thr Val Phe Ser Leu Asn Thr Thr Gly Gly Val Ile Leu Glu Ile Ser Cys Tyr Asn Asp Thr Val Ser Glu Ser Ser Phe Tyr Ser Tyr Gly Glu Ile Ser Phe Gly Val Thr Asp Gly 85 390 395 4

Pro Arg Tyr Cys Phe Ala Leu Tyr Asn Gly Thr Ala Leu Lys Tyr Leu 405 410 415

Gly Thr Leu Pro Pro Ser Val Lys Glu Ile Ala Ile Ser Lys Trp Gly 420 425 430

His Phe Tyr Ile Asn Gly Tyr Asn Phe Phe Ser Thr Phe Pro Ile Asp 435 440 445

Cys Ile Ser Phe Asn Leu Thr Thr Gly Asp Ser Gly Ala Phe Trp Thr 450 455 460

Ile Ala Tyr Thr Ser Tyr Thr Asp Ala Leu Val Gln Val Glu Asn Thr 465 470 475 480

Ala Ile Lys Lys Val Thr Tyr Cys Asn Ser His Ile Asn Asn Ile Lys 485 490 495

Cys Ser Gln Leu Thr Ala Asn Leu Gln Asn Gly Phe Tyr Pro Val Ala 500 505 510

Ser Ser Glu Val Gly Leu Val Asn Lys Ser Val Val Leu Leu Pro Ser 515 520 525

Phe Tyr Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly Met Lys 530 535

Arg Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu Ser Asn Ile Thr 545 550 555 560

Leu Pro Met Gln Asp Asn Asn Thr Asp Val Tyr Cys Ile Arg Ser Asn 565 570 575

Arg Phe Ser Val Tyr Phe His Ser Thr Cys Lys Ser Ser Leu Trp Asp 580 585 590

Asp Val Phe Asn Ser Asp Cys Thr Asp Val Leu Tyr Ala Thr Ala Val 595 600 605

Ile Lys Thr Gly Thr Cys Pro Phe Ser Phe Asp Lys Leu Asn Asn Tyr 610 615 620

Leu Thr Phe Asn Lys Phe Cys Leu Ser Leu Asn Pro Val Gly Ala Asn 625 630 635 640

Cys Lys Phe Asp Val. Ala Ala Arg Thr Arg Thr Asn Glu Gln Val Val
645 650 655

- Arg Ser Leu Tyr Val 1le Tyr Glu Glu Gly Asp Asn Ile Val Gly Val 660 665 670
- Pro Ser Asp Asn Ser Gly Leu His Asp Leu Ser Val Leu His Leu Asp 675 680 685
- Ser Cys Thr Asp Tyr Asn Ile Tyr Gly Ile Thr Gly Val Gly Ile Ile
  690 695 700
- Arg Gln Thr Asn Ser Thr Leu Leu Ser Gly Leu Tyr Tyr Thr Ser Leu 705 710 715 720
- Ser Gly Asp Leu Leu Gly Phe Lys Asn Val Ser Asp Gly Val Ile Tyr
  725 730 735
- Ser Val Thr Pro Cys Asp Val Ser Ala His Ala Ala Val Ile Asp Gly
  740 745 750
- Ala Ile Val Gly Ala Met Thr Ser Ile Asn Ser Glu Leu Leu Gly Leu 755 760 765
- Thr His Trp Thr Thr Pro Asn Phe Tyr Tyr Tyr Ser Ile Tyr Asn 770 775 780
- Tyr Thr Asn Glu Arg Thr Arg Gly Thr Ala Ile Asp Ser Asn Asp Val785 790 795 800
- Asp Cys Glu Pro Ile Ile Thr Tyr Ser Asn Ile Gly Val Cys Lys Asn 805 810 815
- Gly Ala Leu Val Phe Ile Asn Val Thr His Ser Asp Gly Asp Val Gln 820 825 830
- Pro Ile Ser Thr Gly Asn Val Thr Ile Pro Thr Asn Phe Thr Ile Ser 835 840 845
- Val Gln Val Glu Tyr Ile Gln Val Tyr Thr Thr Pro Val Ser Ile Asp 850 860
- Cys Ser Arg Tyr Val Cys Asn Gly Asn Pro Arg Cys Asn Lys Leu Leu 865 870 875 880

Thr Gln Tyr Val Ser Ala Cys Gln Thr Ile Glu Gln Ala Leu Ala Met 885 890 895

- Gly Ala Arg Leu Glu Asn Met Glu Ile Asp Ser Met Leu Phe Val Ser 900 905 910
- Glu Asn Ala Leu Lys Leu Ala Ser Val Glu Ala Phe Asn Ser Thr Glu 915 920 925
- Thr Leu Asp Pro Ile Tyr Lys Glu Trp Pro Asn Ile Gly Gly Ser Trp 930 940
- Leu Gly Gly Leu Lys Asp Ile Leu Pro Ser His Asn Ser Lys Arg Lys 945 955 960
- Tyr Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp Lys Val Val Thr Ser 965 970 975
- Gly Leu Gly Thr Val Asp Glu Asp Tyr Lys Arg Cys Thr Gly Gly Tyr 980 985 990
- Asp Ile Ala Asp Leu Val Cys Ala Gln Tyr Tyr Asn Gly Ile Met Val 995 1000 1 1005
- Leu Pro Gly Val Ala Asn Asp Asp Lys Met Ala Met Tyr Thr Ala 1010 1015 1020
- Ser Leu Ala Gly Gly Ile Thr Leu Gly Ser Leu Gly Gly Gly Ala 1025 1030 1035
- Val Ser Ile Pro Phe Ala Ile Ala Val Gln Ala Arg Leu Asn Tyr 1040 1045 1050
- Val Ala Leu Gln Thr Asp Val Leu Asn Lys Asn Gln Gln Ile Leu 1055 1060 1065
- Ala Asn Ala Phe Asn Gln Ala Ile Gly Asn Ile Thr Gln Ala Phe 1070 1075 1080
- Gly Lys Val Asn Asp Ala Ile His Gln Thr Ser Gln Gly Leu Ala 1085 1090 1095
- Thr Val Ala Lys Val Leu Ala Lys Val Gln Asp Val Val Asn Thr 1100 1105 1110

Gln Gly Gln Ala Leu Ser His Leu Thr Leu Gln Leu Gln Asn Asn 1115 1120 1125

- Phe Gln Ala Ile Ser Ser Ser Ile Ser Asp Ile Tyr Asn Arg Leu 1130 1140
- Asp Glu Leu Ser Ala Asp Ala Gln Val Asp Arg Leu Ile Fhr Gly 1145 1150 1155
- Arg Leu Thr Ala Leu Asn Ala Phe Val Ser Gln Thr Leu Thr Arg 1160 1165 1170
- Gln Ala Glu Val Arg Ala Ser Arg Gln Leu Ala Lys Asp Lys Val 1175 1180 1185
- Asn Glu Cys Val Arg Ser Gln Ser Gln Arg Phe Gly Phe Cys Gly 1190 1200
- Asn Gly Thr His Leu Phe Ser Leu Ala Asn Ala Ala Pro Asn Gly 1205 1210 1215
  - Met Ile Phe Phe His Thr Val Leu Leu Pro Thr Ala Tyr Glu Thr 1220 1225 1230
  - Val Thr Ala Trp Ser Gly Ile Cys Ala Ser Asp Gly Asp Arg Thr 1235 1240 1245
  - Phe Gly Leu Val Val Lys Asp Val Gln Leu Thr Leu Phe Arg Asn 1250 1255 1260
  - Leu Asp Asp Lys Phe Tyr Leu Thr Pro Arg Thr Met Tyr Gln Pro 1265 1270 1275
  - Ile Val Ala Thr Ser Ser Asp Phe Val Gln Ile Glu Gly Cys Asp 1280 1285 1290
  - Val Leu Phe Val Asn Ala Thr Val Ile Asp Leu Pro Ser Ile Ile 1295 1300 1305
    - Pro Asp Tyr Ile Asp Ile Asn Gln Thr Val Gln Asp Ile Leu Glu 1310 1315 1320
    - Asn Phe Arg Pro Asn Trp Thr Val Pro Glu Leu Pro Leu Asp Ile 1325 1330 1335
    - Phe Asn Ala Thr Tyr Leu Asn Leu Thr Gly Glu Ile Asn Asp Leu

1345

1350

Glu Phe Arg Ser Glu Lys Leu His Asn Thr Thr Val Glu Leu Ala 1355 1360 1365

Ile Leu Ile Asp Asn Ile Asn Asn Thr Leu Val Asn Leu Glu Trp 1370 1375 1380

Leu Asn Arg Ile Glu Thr Tyr Val Lys Trp Pro Trp Tyr Val Trp 1385 1390 1395

Leu Leu Ile Gly Leu Val Val Ile Phe Cys Ile Pro Ile Leu Leu 1400 1410

Phe Cys Cys Cys Ser Thr Gly Cys Cys Gly Cys Ile Gly Cys Leu 1415 1420 1425

Gly Ser Cys Cys His Ser Ile Cys Ser Arg Arg Gln Phe Glu Ser 1430 1435 1440

Tyr Glu Pro Ile Glu Lys Val His Val His 1445 1450

<210> 56

<211> 1464

<212> PRT

<213> Feline infectious peritonitis virus

<400> 56

Met Ile Phe Ile Ile Leu Thr Leu Leu Ser Val Ala Lys Ser Glu Asp 1 5 10 15

Ala Pro His Gly Val Thr Leu Pro Gln Phe Asn Thr Ser His Asn Asn 20 25 30

Glu Arg Phe Glu Leu Asn Phe Tyr Asn Phe Leu Gln Thr Trp Asp Ile 35 40 45

Pro Pro Asn Thr Glu Thr Ile Leu Gly Gly Tyr Leu Pro Tyr Cys Gly 50 55 60

Ala Gly Val Asn Cys Gly Trp Tyr Asn Phe Ser Gln Ser Val Gly Gln 65 70 75 80

Asn Gly Lys Tyr Ala Tyr Ile Asn Thr Gln Asn Leu Asn Ile Pro Asn 85 90 95

. . .

Val His Gly Val Tyr Phe Asp Val Arg Glu His Asn Asn Asp Gly Glu 100 105 110 Trp Asp Asp Arg Asp Lys Val Gly Leu Leu Ile Ala Ile His Gly Asn 115 120 125 Ser Lys Tyr Ser Leu Leu Met Val Leu Gln Asp Ala Val Glu Ala Asn 130 135 140 Gln Pro His Val Ala Val Lys Ile Cys His Trp Lys Pro Gly Asn Ile Ser Ser Tyr His Ala Phe Ser Val Asn Leu Gly Asp Gly Gln Cys , 165 170 175 Val Phe Asn Gln Arg Phe Ser Leu Asp Thr Val Leu Thr Thr Asn Asp 180 185 Phe Tyr Gly Phe Gln Trp Thr Asp Thr Tyr Val Asp Ile Tyr Leu Gly 195 200 205 Gly Thr Ile Thr Lys Val Trp Val Asp Asn Asp Trp Ser Ile Val Glu 210 215 220 Ala Ser Ile Ser Tyr His Trp Asn Arg Ile Asn Tyr Gly Tyr Tyr Met 225 230 235 240 Gln Phe Val Asn Arg Thr Thr Tyr Tyr Ala Tyr Asn Asn Thr Gly Gly 250 255 Ala Asn Tyr Thr Gln Leu Gln Leu Ser Glu Cys His Thr Asp Tyr Cys 265 Ala Gly Tyr Ala Lys Asn Val Phe Val Pro Ile Asp Gly Lys Ile Pro 275 280 285 Glu Asp Phe Ser Phe Ser Asn Trp Phe Leu Leu Ser Asp Lys Ser Thr 295 Leu Val Gln Gly Arg Val Leu Ser Ser Gln Pro Val Phe Val Gln Cys 310 315 Leu Arg Pro Val Pro Ser Trp Ser Asn Asn Thr Ala Val Val His Phe

330

325 .

Lys Asn Asp Ala Phe Cys Pro Asn Val Thr Ala Asp Val Leu Arg Phe 345 350 Asn Leu Asn Phe Ser Asp Thr Asp Val Tyr Thr Asp Ser Thr Asn Asp . 360 Glu Gln Leu Phe Phe Thr Phe Glu Asp Asn Thr Thr Ala Ser Ile Ala 375 - 380 Cys Tyr Ser Ser Ala Asn Val Thr Asp Phe Gln Pro Ala Asn Asn Ser 385 390 395 400 Val Ser His Ile Pro Phe Gly Lys Thr Ala His Phe Cys Phe Ala Asn 405 410 Phe Ser His Ser Ile Val Ser Arg Gln Phe Leu Gly Ile Leu Pro Pro 420 425 430 Thr Val Arg Glu Phe Ala Phe Gly Arg Asp Gly Ser Ile Phe Val Asn 435 440 Gly Tyr Lys Tyr Phe Ser Leu Pro Ala Ile Arg Ser Val Asn Phe Ser 450 455 460 Ile Ser Ser Val Glu Glu Tyr Gly Phe Trp Thr Ile Ala Tyr Thr Asn 465 470 475 480 Tyr Thr Asp Val Met Val Asp Val Asn Gly Thr Ala Ile Thr Arg Leu 485 490 495 Phe Tyr Cys Asp Ser Pro Leu Asn Arg Ile Lys Cys Gln Gln Leu Lys 500 505 His Glu Leu Pro Asp Gly Phe Tyr Ser Ala Ser Met Leu Val Lys Lys 515 520 525 Asp Leu Pro Lys Thr Phe Val Thr Met Pro Gln Phe Tyr His Trp Met 530 Asn Val Thr Leu His Val Val Leu Asn Asp Thr Glu Lys Lys Tyr Asp 545 550 <u>555</u>

Ile Ile Leu Ala Lys Ala Pro Glu Leu Ala Ala Leu Ala Asp Val His
565 570 575

Phe Glu Ile Ala Gln Ala Asn Gly Ser Val Thr Asn Val Thr Ser Leu

585

590

- Cys Val Gln Ala Arg Gln Leu Ala Leu Phe Tyr Lys Tyr Thr Ser Leu 595 600 605
- Gln Gly Leu Tyr Thr Tyr Ser Asn Leu Val Glu Leu Gln Asn Tyr Asp 610 615 620
- Cys Pro Phe Ser Pro Gln Gln Phe Asn Asn Tyr Leu Gln Phe Glu Thr 625 630 635 640
- Leu Cys Phe Asp Val Asn Pro Ala Val Ala Gly Cys Lys Trp Ser Leu 645 650 655
- Val His Asp Val Gln Trp Arg Thr Gln Phe Ala Thr Ile Thr Val Ser 660 665 670
- Tyr Lys His Gly Ser Met Ile Thr Thr His Ala Lys Gly His Ser Trp
  675 680 685
- Gly Phe Gln Asp Thr Ser Val Leu Val Lys Asp Glu Cys Thr Asp Tyr 690 695 700
- Asn Ile Tyr Gly Phe Gln Gly Thr Gly Ile Ile Arg Asn Thr Thr Ser 705 710 715 720
- Arg Leu Val Ala Gly Leu Tyr Tyr Thr Ser Ile Ser Gly Asp Leu Leu 725 730 735
- Ala Phe Lys Asn Ser Thr Thr Gly Glu Ile Phe Thr Val Val Pro Cys
  740 745 750
- Asp Leu Thr Ala Gln Val Ala Val Ile Asn Asp Glu Ile Val Gly Ala 755 760 765
- Ile Thr Ala Val Asn Gln Thr Asp Leu Phe Glu Phe Val Asn Asn Thr
  770 775 780
- Gln Ala Arg Arg Ser Arg Ser Ser Thr Pro Asn Phe Val Thr Ser Tyr 785 790 795 800
- Thr Met Pro Gln Phe Tyr Tyr Ile Thr Lys Trp Asn Asn Asp Thr Ser 805 810 815
- Ser Asn Cys Thr Ser Ala Ile Thr Tyr Ser Ser Phe Ala Ile Cys Asn 820 825 830

Thr Gly Glu Ile Lys Tyr Val Asn Val Thr His Val Glu Ile Val Asp 835 840 845

- Asp Ser Ile Gly Val Ile Lys Pro Val Ser Thr Gly Asn Ile Ser Ile 850 855 860
- Pro Lys Asn Phe Thr Val Ala Val Gln Ala Glu Tyr Ile Gln Ile Gln 865 870 875 880
- Val Lys Pro Val Val Val Asp Cys Ala Thr Tyr Val Cys Asn Gly Asn 885 890 895
- Thr His Cys Leu Lys Leu Leu Thr Gln Tyr Thr Ser Ala Cys Gln Thr
  900 905 910
  - Ile Glu Asn Ala Leu Asn Leu Gly Ala Arg Leu Glu Ser Leu Met Leu 915 920 925
- Asn Asp Met Ile Thr Val Ser Asp Arg Gly Leu Glu Leu Ala Thr Val 930 935 940
- Glu Arg Phe Asn Ala Thr Ala Leu Gly Gly Glu Lys Leu Gly Gly Leu 945 , 950 955 960
- Tyr Phe Asp Gly Leu Ser Ser Leu Leu Pro Pro Lys Ile Gly Lys Arg 965 970 975
- Ser Ala Val Glu Asp Leu Leu Phe Asn Lys Val Val Thr Ser Gly Leu 980 985 990
- Gly Thr Val Asp Asp Asp Tyr Lys Lys Cys Ser Ser Gly Thr Asp Val 995 1000 1005
- Ala Asp Leu Val Cys Ala Gln Tyr Tyr Asn Gly Ile Met Val Leu 1010 1015 1020
- Pro Gly Val Val Asp Gly Asn Lys Met Ser Met Tyr Thr Ala Ser 1025 1030 1035
- Leu Ile Gly Gly Met Ala Leu Gly Ser Ile Thr Ser Ala Val Ala 1040 1045 1050
- Val Pro Phe Ala Met Gln Val Gln Ala Arg Leu Asn Tyr Val Ala 1055 1060 1065

Leu Gln Thr Asp Val Leu Gln Glu Asn Gln Lys Ile Leu Ala Asn 1070 1075 1080 Ala Phe Asn Asn Ala Ile Gly Asn Ile Thr Leu Ala Leu Gly Lys 1085 1090 1095 Val Ser Asn Ala Ile Thr Thr Thr Ser Asp Gly Phe Asn Ser Met 1100 1105 1110 Ala Ser Ala Leu Thr Lys Ile Gln Ser Val Val Asn Gln Gln Gly 1115 1120 1125 Glu Ala Leu Ser Gln Leu Thr Ser Gln Leu Gln Lys Asn Phe Gln 1130 1135 1140 Ala Ile Ser Ser Ser Ile Ala Glu Ile Tyr Asn Arg. Leu Glu Lys 1145 1150 1155 Val Glu Ala Asp Ala Gln Val Asp Arg Leu Ile Thr Gly Arg Leu 1160 1165 1170 Ala Ala Leu Asn Ala Tyr Val Ser Gln Thr Leu Thr. Gln Tyr Ala 1175 1180 1185 Glu Val Lys Ala Ser Arg Gln Ile Ala Leu Glu Lys Val Asn Glu Cys Val Lys Ser Gln Ser Asn Arg Tyr Gly Phe Cys Gly Asn Gly 1215 1210 Thr His Leu Phe Ser Leu Val Asn Ser Ala Pro Glu Gly Leu Leu 1220 1225 Phe Phe His Thr Val Leu Leu Pro Thr Glu Trp Glu Glu Val Thr 1240 1245 Ala Trp Ser Gly Ile Cys Val Asn Asp Thr Tyr Ala Tyr Val Leu 1255 1260 Lys Asp Phe Asp His Ser Ile Phe Ser Tyr Asn Gly Thr Tyr Met 1265 1270 Val Thr Pro Arg Asn Met Phe Gln Pro Arg Lys Pro Gln Met Ser 1285

WO 2004/096842 PCT/CA2004/000626

Asp Phe Val Gln Ile Thr Ser Cys Glu Val Thr Phe Leu Asn Met 1295 1300 1305

- Thr Tyr Thr Thr Phe Gln Glu Ile Val Ile Asp Tyr Ile Asp Ile 1310 1315 1320
- Asn Lys Thr Ile Ala Asp Met Leu Glu Gln Tyr Asn Pro Asn Tyr 1325. 1330 1335
- Thr Thr Pro Glu Leu Asn Leu Leu Leu Asp Ile Phe Asn Gln Thr 1340 1345 1350
- Lys Leu Asn Leu Thr Ala Glu Ile Asp Gln Leu Glu Gln Arg Ala 1355 1360 1365
- Asp Asn Leu Thr Thr Ile Ala His Glu Leu Gln Gln Tyr Ile Asp 1370 1375 1380
- Asn Leu Asn Lys Thr Leu Val Asp Leu Asp Trp Leu Asn Arg Ile 1385 1390 1395
- Glu Thr Tyr Val Lys Trp Pro Trp Tyr Val Trp Leu Leu Ile Gly
  1400 1405
- Leu Val Val Val Phe Cys Ile Pro Leu Leu Phe Cys Cys Leu 1415 1420 1425
- Ser Thr Gly Phe Cys Gly Cys Phe Gly Cys Val Gly Ser Cys Cys 1430 1440
- His Ser Leu Cys Ser Arg Arg Gln Phe Glu Thr Tyr Glu Pro Ile 1445 1450 1455
- Glu Lys Val His Ile His
- <210> 57
- <211> 1235
- <212> PRT
- <213> Mouse hepatitis virus
- <400> 57
- Met Leu Phe Val Phe Ile Leu Leu Pro Ser Cys Leu Gly Tyr Ile
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- Gly Asp Phe Arg Cys Ile Gln Thr Val Asn Tyr Asn Gly Asn Asn Ala 20 25 30

Ser Ala Pro Ser Ile Ser Thr Glu Ala Val Asp Val Ser Lys Gly Arg
35 40 45

- Gly Thr Tyr Tyr Val Leu Asp Arg Val Tyr Leu Asn Ala Thr Leu Leu 50 55 60
- Leu Thr Gly Tyr Tyr Pro Val Asp Gly Ser Asn Tyr Arg Asn Leu Ala 65 70 75 80
- Leu Thr Gly Thr Asn Thr Leu Ser Leu Thr Trp Phe Lys Pro Pro Phe 85 90 95
- Leu Ser Glu Phe Asn Asp Gly Ile Phe Ala Lys Val Gln Asn Leu Lys
  100 105 110
- Thr Asn Thr Pro Thr Gly Ala Thr Ser Tyr Phe Pro Thr Ile Val Ile 115 120 125.
- Gly Ser Leu Phe Gly Asn Thr Ser Tyr Thr Val Val Leu Glu Pro Tyr 130 135 140
- Asn Asn Ile Ile Met Ala Ser Val Cys Thr Tyr Thr Ile Cys Gln Leu 145 . 150 155 160
- Pro Tyr Thr Pro Cys Lys Pro Asn Thr Asn Gly Asn Arg Val Ile Gly 165 170 175
- Phe Trp His Thr Asp Val Lys Pro Pro Ile Cys Leu Leu Lys Arg Asn 180 185
- Phe Thr Phe Asn Val Asn Ala Pro Trp Leu Tyr Phe His Phe Tyr Gln 195 200 205
- Gln Gly Gly Thr Phe Tyr Ala Tyr Tyr Ala Asp Lys Pro Ser Ala Thr 210 215 220
- Thr Phe Leu Phe Ser Val Tyr Ile Gly Asp Ile Leu Thr Gln Tyr Phe 225 230 235 240
- Val Leu Pro Phe Ile Cys Thr Pro Thr Ala Gly Ser Thr Leu Ala Pro 245 250 255
- Leu Tyr Trp Val Thr Pro Leu Leu Lys Arg Gln Tyr Leu Phe Asn Phe 260 265 270

Asn Glu Lys Gly Val Ile Thr Ser Ala Val Asp Cys Ala Ser Ser Tyr 275 280 285 Ile Ser Glu Ile Lys Cys Lys Thr Gln Ser Leu Leu Pro Ser Thr Gly 290 . 295 Val Tyr Asp Leu Ser Gly Tyr Thr Val Gln Pro Val Gly Val Tyr 310 315 Arg Arg Val Pro Asn Leu Pro Asp Cys Lys Ile Glu Glu Trp Leu Thr 325 330 335 Ala Lys Ser Val Pro Ser Pro Leu Asn Trp Glu Arg Arg Thr Phe Gln 345 Asn Cys Asn Phe Asn Leu Ser Ser Leu Leu Arg Tyr Val Gln Ala Glu 355 360 365 Ser Leu Ser Cys Asn Asn Ile Asp Ala Ser Lys Val Tyr Gly Met Cys 380 Phe Gly Ser Val Ser Val Asp Lys Phe Ala Ile Pro Arg Ser Arg Gln 385 390 395 400 Ile Asp Leu Gln Ile Gly Asn Ser Gly Phe Leu Gln Thr Ala Asn Tyr 405 410 Lys Ile Asp Thr Ala Ala Thr Ser Cys Gln Leu Tyr Tyr Ser Leu Pro 420 425 430 Lys Asn Asn Val Thr Ile Asn Asn Tyr Asn Pro Ser Ser Trp Asn Arg 440 Arg Tyr Gly Phe Lys Val Asn Asp Arg Cys Gln Ile Phe Ala Asn Ile 450 455 460 Leu Leu Asn Gly Ile Asn Ser Gly Thr Thr Cys Ser Thr Asp Leu Gln Leu Pro Asn Thr Glu Val Ala Thr Gly Val Cys Val Arg Tyr Asp Leu 490 Tyr Gly Ile Thr Gly Gln Gly Val Phe Lys Glu Val Lys Ala Asp Tyr Tyr Asn Ser Trp Gln Ala Leu Leu Tyr Asp Val Asn Gly Asn Leu Asn 515 525

- Gly Phe Arg Asp Leu Thr Thr Asn Lys Thr Tyr Thr Ile Arg Ser Cys 530 535
- Tyr Ser Gly Arg Val Ser Ala Ala Tyr His Lys Glu Ala Pro Glu Pro 545 550 555 560

4.09

- Ala Leu Leu Tyr Arg Asn Ile Asn Cys Ser Tyr Val Phe Thr Asn Asn 565 570 575
- Ile Ser Arg Glu Glu Asn Pro Leu Asn Tyr Phe Asp Ser Tyr Leu Gly 580 585 590
- Cys Val Val Asn Ala Asp Asn Arg Thr Asp Glu Ala Leu Pro Asn Cys 595 600 605
  - Asn Leu Arg Met Gly Ala Gly Leu Cys Val Asp Tyr Ser Lys Ser Arg 610 615 620
  - Arg Ala Arg Arg Ser Val Ser Thr Gly Tyr Arg Leu Thr Thr Phe Glu 625 630 635 640
  - Pro Tyr Met Pro Met Leu Val Asn Asp Ser Val Gln Ser Val Gly Gly 645 650 655
  - Leu Tyr Glu Met Gln Ile Pro Thr Asn Phe Thr Ile Gly His His Glu 660 665 670
  - Glu Phe Ile Gln Ile Arg Ala Pro Lys Val Thr Ile Asp Cys Ala Ala 675 680 685
  - Phe Val Cys Gly Asp Asn Ala Ala Cys Arg Gln Gln Leu Val Glu Tyr 690 695 700
  - Gly Ser Phe Cys Asp Asn Val Asn Ala Ile Leu Asn Glu Val Asn Asn 705 710 715 720
  - Leu Leu Asp Asn Met Gln Leu Gln Val Ala Ser Ala Leu Met Gln Gly 725 730 735
  - Val Thr Ile Ser Ser Arg Leu Pro Asp Gly Ile Ser Gly Pro Ile Asp
    740 745
  - Asp Ile Asn Phe Ser Pro Leu Leu Gly Cys Ile Gly Ser Thr Cys Ala

760

76

Glu Asp Gly Asn Gly Pro Ser Ala Ile Arg Gly Arg Ser Ala Ile Glu 770 775 780

Asp Leu Leu Phe Asp Lys Val Lys Leu Ser Asp Val Gly Phe Val Glu 785 790 795 800

Ala Tyr Asn Asn Cys Thr Gly Gly Gln Glu Val Arg Asp Leu Leu Cys 805 810 815

Val Gln Ser Phe Asn Gly Ile Lys Val Leu Pro Pro Val Leu Ser Glu 820 825 830

Ser Gln Ile Ser Gly Tyr Thr Ala Gly Ala Thr Ala Ala Ala Met Phe 835 840 845

Pro Pro Trp Thr Ala Ala Ala Gly Val Pro Phe Ser Leu Asn Val Gln 850 855 860

Tyr Arg Ile Asn Gly Leu Gly Val Thr Met Asn Val Leu Ser Glu Asn 865 870 875 880

Gln Lys Met Ile Ala Ser Ala Phe Asn Asn Ala Leu Gly Ala Ile Gln 885 890 895

1

Glu Gly Phe Asp Ala Thr Asn Ser Ala Leu Gly Lys Ile Gln Ser Val 900 905 910

Val Asn Ala Asn Ala Glu Ala Leu Asn Asn Leu Leu Asn Gln Leu Ser 915 920 925

Asn Arg Phe Gly Ala Ile Ser Ala Ser Leu Gln Glu Ile Leu Thr Arg 930 935 940

Leu Asp Ala Val Glu Ala Lys Ala Gln Ile Asp Arg Leu Ile Asn Gly 945 950 955 960

Arg Leu Thr Ala Leu Asn Ala Tyr Ile Ser Lys Gln Leu Ser Asp Ser 965 970 975

Thr Leu Ile Lys Phe Ser Ala Ala Gln Ala Ile Glu Lys Val Asn Glu 980 985 990

Cys Val Lys Ser Gln Thr Thr Arg Ile Asn Phe Cys Gly Asn Gly Asn 995 1000 1005 WO 2004/096842 PCT/CA2004/000626

His Ile Leu Ser Leu Val Gln Asn Ala Pro Tyr Gly Leu Cys Phe 1010 1015 1020 Ile His Phe Ser Tyr Val Pro Thr Ser Phe Lys Thr Ala Asn Val 1025 1030 1035 Ser Pro Gly Leu Cys Ile Ser Gly Asp Arg Gly Leu Ala Pro Lys 1040 1045 Ala Gly Tyr Phe Val Gln Asp Asn Gly Glu Trp Lys Phe Thr Gly 1055 1060 1065 Ser Asn Tyr Tyr Tyr Pro Glu Pro Ile Thr Asp Lys Asn Ser Val 1075 1080 1070 Ala Met Ile Ser Cys Ala Val Asn Tyr Thr Lys Ala Pro Glu Val 1085 1090 1095<sup>.</sup> Phe Leu Asn Asn Ser Ile Pro Asn Leu Pro Asp Phe Lys Glu Glu 1100 1105 1110 Leu Asp Lys Trp Phe Lys Asn Gln Thr Ser Ile Ala Pro Asp Leu 1115 1120 1125 Ser Leu Asp Phe Glu Lys Leu Asn Val Thr Phe Leu Asp Leu Thr 1130 1135 1140 Tyr Glu Met Asn Arg Ile Gln Asp Ala Ile Lys Lys Leu Asn Glu . 1145 1150 1155 Ser Tyr Ile Asn Leu Lys Glu Val Gly Thr Tyr Glu Met Tyr Val 1160 1165 Lys Trp Pro Trp Tyr Val Trp Leu Leu Ile Gly Leu Ala Gly Val 1175 1180 1185 Ala Val Cys Val Leu Leu Phe Phe Ile Cys Cys Cys Thr Gly Cys 1190 1195 1200 Gly Ser Cys Cys Phe Arg Lys Cys Gly Ser Cys Cys Asp Glu Tyr 1205 1210 Gly Gly His Gln Asp Ser Ile Val Ile His Asn Ile Ser Ala His 1220 1225

. Glu Asp 1235

<210> 58

<211> 1363

<212> PRT

<213> human coronavirus

<400> 58

Met Phe Leu Ile Leu Leu Ile Ser Leu Pro Met Ala Leu Ala Val Ile 1 5 10 15 ,

Gly Asp Leu Lys Cys Thr Thr Val Ala Ile Asn Asp Val Asp Thr Gly 20 25 30

Val Pro Ser Thr Ser Thr Asp Ile Val Asp Val Thr Asn Gly Leu Gly
35 40 45

Thr Tyr Tyr Val Leu Asp Arg Val Tyr Leu Asn Thr Thr Leu Leu Leu 50 55 60

Asn Gly Tyr Tyr Pro Thr Ser Gly Ser Thr Tyr Arg Asn Met Ala Leu 65 70 75 80

Lys Gly Thr Leu Leu Leu Ser Arg Leu Trp Phe Lys Pro Pro Phe Leu 85 90 95

Ser Asp Phe Ile Asn Gly Ile Phe Ala Lys Val Lys Asn Thr Lys Val 100 105 110

Ile Lys His Gly Val Met Tyr Ser Glu Phe Pro Ala Ile Thr Ile Gly 115 120 125

Ser Thr Phe Val Asn Thr Ser Tyr Ser Val Val Val Gln Pro His Thr 130 140

Thr Asn Leu Asp Asn Lys Leu Gln Gly Leu Leu Glu Ile Ser Val Cys 145 150 155 160

Gln Tyr Thr Met Cys Glu Tyr Pro Asn Thr Ile Cys His Pro Asn Leu 165 170 175

Gly Asn Arg Arg Val Glu Leu Trp His Trp Asp Thr Gly Val Val Ser 180 185 190

Cys Leu Tyr Lys Arg Asn Phe Thr Tyr Asp Val Asn Ala Asp Tyr Leu

. 195 . 200

205

										•	-	203			
Tvr	Phe	His	Phe	Tvr	Gln	Glu	Glv	Gly	TIÉ	Phe	Tur	Δ1 =	ጥ <b>v</b> r	Phe	Thr
	210		20	-1-	,	215	:	GIY.	110	Liic	220			·	
Asp 225	Thr	Gly	Val'	'Val	Thr 230	Lys	Phe	Leu	Phe	Asn 235	Val	Tyr	Leu	Gly	Thr- 240
Val	Leu	Ser	Tyr	Tyr 245	Ťyr	Val	Met	Pro	Leu 250	Thr	Суз	Asn	Ser	Ala 255	Met
Thr	Leu	Glu	Tyr 260	Trp	Val	Thr	Pro	Leu 265	Thr	Ser	Lys	Gln	Tyr 270	Leu	Leu
Ala	Phe	Asn 275	Gln	Asp	Gly	Val	Ile 280	Phe	Asn	Ala	Val	Asp 285	Cys	ràs'	Ser
Asp	Phe 290	Met	Ser	Glu	Ile	Lys 295	Cys	Lys	Thr	Leu	Ser 300	Ile	Ala	Pro	Ser
Thr 305	Gly	Val	Tyr	Glu	Leu 310	Asn	Gly	Tyr		Val 315	Gln	Pro	Ile	Ala	Asp 320
Val	Tyr	Arg	Arg	Ile 325	Pro	Asn	Leu	Pro	Asp 330	Cys	Asn	Tle	Glu	Ala 335	Trp
Leu	Asn	Asp	Lys 340	Ser	Val	Pro	Ser	Pro 345	Leu	Asn	Trp	Glu	Arg 350	Lys	Thr <sub>.</sub>
Phe	Ser	Asn 355	Cys	Asn	Phe	Asn	Met 360	·Ser	Ser	Leu	Met	Ser 365	Phe	Ile	Gln
Ala	Asp 370	Ser	Phe	Thr		Asn 375	Asn	Ile	Asp	Ala	Ala 380	Lys	Ile	Tyr	Gly
Met 385	Cys	Phe	Ser	Ser	lle 390	Thr	Ile	Asp	Lys	Phe 395	Ala	Ile	Pro	Asn	Gly 400
Arg	Lys	Val	Asp	Leu 405	Gln	Leu	Gly	Asn	Leu 410	Gly	Tyr	Leu	Gln	Ser 415	Phe
Asn	Tyr	Arg	Ile 420	Asp	Thr	Thr	Ala	Thr 425	Ser	Cys	Gln	Leu	Tyr 430	Tyr	Asn
Leu	Pro	Ala 435		Asn	Val	Ser	Val 440		Arg	Phe	Asn	Pro .445	Ser	Ile	Trp

- Asn Arg Arg Phe Gly Phe Thr Glu Gln Ser Val Phe Lys Pro Gln Pro 450 455 460
- Ala Gly Val Phe Thr Asp His Asp Val Val Tyr Ala Gln His Cys Phe 465 470 475 480
- Lys Ala Pro Thr Asn Phe Cys Pro Cys Lys Leu Asp Gly Ser Leu Cys
  485 490 495
- Val Gly Asn Gly Pro Gly Ile Asp Ala Gly Tyr Lys Asn Ser Gly Ile 500 505 510
- Gly Thr Cys Pro Ala Gly Thr Asn Tyr Leu Thr Cys His Asn Ala Val 515 520 525
- Gln Cys Asn Cys Leu Cys Thr Pro Asp Pro Ile Thr Ser Lys Ser Thr 530 540
- Gly Pro Tyr Lys Cys Pro Gln Thr Lys Tyr Leu Val Gly Ile Gly Glu 545 550 555 560
- His Cys Ser Gly Leu Ala Ile Lys Ser Asp Tyr Cys Gly Gly Asn Pro 565 570 575
- Cys Thr Cys Gln Pro Gln Ala Phe Leu Gly Trp Ser Val Asp Ser Cys 580 585 590
- Leu Gln Gly Asp Arg Cys Asn Ile Phe Ala Asn Phe Ile Leu His Asp 595 600 605
- Val Asn Ser Gly Thr Thr Cys Ser Thr Asp Leu Gln Lys Ser Asn Thr 610 615 620
- Asp Ile Ile Leu Gly Val Cys Val Asn Tyr Asp Leu Tyr Gly Ile Thr 625 630 635 640
- Gly Gln Gly Ile Phe Val Glu Val Asn Ala Pro Tyr Tyr Asn Ser Trp
  645 650 655
- Gln Asn Leu Leu Tyr Asp Ser Asn Gly Asn Leu Tyr Gly Phe Arg Asp 660 665 670
- Tyr Leu Thr Asn Arg Thr Phe Met Ile Arg Ser Cys Tyr Ser Gly Arg 675 680 685

Val Ser Ala Ala Phe His Ala Asn Ser Ser Glu Pro Ala Leu Leu Phe 690 695 700.

- Arg Asn Ile Lys Cys Asn Tyr Val Phe Asn Asn Thr Leu Ser Arg Gln 705 710 715 720
- Leu Gln Pro Ile Asn Tyr Phe Asp Ser Tyr Leu Gly Cys Val Val Asn 725 730 735
- Ala Asp Asn Ser Thr Ala Ser Ala Val Gln Thr Cys Asp Leu Thr Val 740 745 750
- Gly Ser Gly Tyr Cys Val Asp Tyr Ser Thr Lys Arg Arg Ser Arg Arg 755 760 765
  - Ala Ile Thr Thr Gly Tyr Arg Phe Thr Asn Phe Glu Pro Phe Thr Val 770 780
  - Asn Ser Val Asn Asp Ser Leu Glu His Val Gly Gly Leu Tyr Glu Ile 785 790 795 800
  - Gln Ile Pro Ser Glu Phe Thr Ile Gly Asn Met Glu Glu Phe Ile Gln 805 · 810 815
  - Thr Ser Ser Pro Lys Val Thr Ile Asp Cys Ser Ala Phe Val Cys Gly 820 825 830
  - Asp Cys Ala Ala Cys Lys Ser Gln Leu Val Glu Tyr Gly Ser Phe Cys 835 840 845
  - Asp Asn Ile Asn Ala Ile Leu Thr Glu Val Asn Glu Leu Leu Asp Thr 850 855 860
  - Thr Gln Leu Gln Val Ala Asn Ser Leu Met Asn Gly Val Thr Leu Ser 865 870 875 880
  - Thr Lys Leu Lys Asp Gly Val Asn Phe Asn Val Asp Asp Val Asn Phe 885 890 895
  - Ser Pro Val Leu Gly Cys Leu Gly Ser Glu Cys Asn Lys Val Ser Ser 900 905 910
  - Arg Ser Ala Ile Glu Asp Leu Leu Phe Ser Lys Val Arg Leu Ser Asp 915 920 925

Val Gly Phe Val Glu Ala Tyr Asn Asn Cys Thr Gly Gly Ala Gly Ile 930 935 940

- Arg Asp Leu Ile Cys Val Gln Ser Tyr Asn Gly Ile Lys Val Leu Pro 945 950 955 960
- Pro Leu Leu Ser Asp Asn Gln Ile Ser Gly Tyr Thr Leu Ala Ala Thr 965 970 975
- Ser Ala Asn Leu Phe Pro Pro Trp Ser Ala Ala Ala Gly Val Pro Phe 980 985 990
- Tyr Leu Asn Val Gln Tyr Arg Ile Asn Gly Ile Gly Val Thr Met Asp 995 1000 1005
- Val Leu Ser Gln Asn Gln Lys Leu Ile Ala Asn Ala Phe Asn Asn 1010 1015 1020
- Ala Leu Asp Ala Ile Gln Glu Gly Phe Asp Ala Thr Asn Ser Ala 1025 1030 1035
- Leu Val Lys Ile Gln Ala Val Val Asn Ala Asp Ala Glu Ala Leu 1040 1045 1050
- Asn Asn Leu Leu Gln Gln Leu Ser Asn Arg Phe Gly Ala Ile Ser 1055 1060 1065
- Ser Ser Leu Gln Glu Ile Leu Ser Arg Leu Asp Ala Leu Glu Ala 1070 1075 1080
- Gln Ala Gln Ile Asp Arg Leu Ile Asn Gly Arg Leu Thr Ala Leu 1085 1090 1095
- Asp Ala Tyr Val Ser Gin Gln Leu Ser Asp Ser Thr Leu Val Lys 1100 1105 1110
- Phe Ser Ala Ala Gln Ala Met Glu Lys Val Asn Glu Cys Val Lys 1115 1120 1125
- Ser Gln Ser Ser Arg Ile Asn Phe Cys Gly Asn Gly Asn His Ile 1130 1135 1140
- Ile Ser Leu Val Gln Asn Ala Pro Tyr Gly Leu Tyr Phe Ile His 1145 1150 1155
- Phe Ser Tyr Val Pro Thr Lys Tyr Val Thr Ala Lys Val Ser Pro

Gly Leu Cys Ile Ala Gly Asp Arg Gly Ile Ala Pro Lys Ser Gly 1175 1180 1185

Tyr Phe Val Ash Val Asn Asn Thr Trp Met Phe Thr Gly Ser Arg 1190 1195 1200 

Tyr Tyr Tyr Pro Glu Pro Ile Thr Gly Asn Asn Val Val Wat 1205 1210 1215

Ser Thr Cys Ala Val Asn Tyr Thr Lys Ala Pro Asp Val Met Leu 1220 1225 1230

Asn Ile Ser Thr Pro Asn Leu Pro Asp Phe Lys Glu Glu Leu Asp 1235 1240 1245

Gln Trp Phe Lys Asn Gln Thr Leu Val Ala Pro Asp Leu Ser Leu 1250 1260

Asp Tyr Ile Asn Val Thr Phe Leu Asp Leu Gln Asp Glu Met Asn 1265 1270 1275

Arg Leu Gln Glu Ala Ile Lys Val Leu Asn Gln Ser Tyr Ile Asn 1280 1285 1290

Leu Lys Asp Ile Gly Thr Tyr Glu Tyr Tyr Val Lys Trp Pro Trp 1300

Tyr Val Trp Leu Leu Ile Gly Phe Ala Gly Val Ala Met Leu Val 1310 1315 1320

Leu Leu Phe Phe Ile Cys Cys Cys Thr Gly Cys Gly Thr Ser Cys 1330

Phe Lys Lys Cys Gly Gly Cys Cys Asp Asp Tyr Thr Gly His Gln 1340 1345

Glu Leu Val Ile Lys Thr Ser His Glu Gly 1355 . 1360

<210> 59

<211> 1383 <212> PRT

<213> Porcine epidemic diarrhea virus

<400> 59

Met Arg Ser Leu Ile Tyr Phe Trp Leu Leu Leu Pro Val Leu Pro Thr 1 5 10 15

- Leu Ser Leu Pro Gln Asp Val Thr Arg Cys Gln Ser Thr Thr Asn Phe
  20 25 30
- Arg Arg Phe Phe Ser Lys Phe Asn Val Gln Ala Pro Ala Val Val 35 40 45
- Leu Gly Gly Tyr Leu Pro Ser Met Asn Ser Ser Ser Trp Tyr Cys Gly 50 55 60
- Thr Gly Ile Glu Thr Ala Ser Gly Val His Gly Ile Phe Leu Ser Tyr 65 70 75 80
- Ile Asp Ser Gly Gln Gly Phe Glu Ile Gly Ile Ser Gln Glu Pro Phe
  85 90 95
- Asp Pro Ser Gly Tyr Gln Leu Tyr Leu His Lys Ala Thr Asn Gly Asn 100 105 110
- Thr Asn Ala Thr Ala Arg Leu Arg Ile Cys Gln Phe Pro Asp Asn Lys
  115 120 125
- Thr Leu Gly Pro Thr Val Asn Asp Val Thr Thr Gly Arg Asn Cys Leu 130 135 140
- Phe Asn Lys Ala Ile Pro Ala Tyr Met Arg Asp Gly Lys Asp Ile Val 145 150 155 160
- Val Gly Ile Thr Trp Asp Asn Asp Arg Val Thr Val Phe Ala Asp Lys
  165 170 175
- Ile Tyr His Phe Tyr Leu Lys Asn Asp Trp Ser Arg Val Ala Thr Arg 180 185
- Cys Tyr Asn Arg Arg Ser Cys Ala Met Gln Tyr Val Tyr Thr Pro Thr 195 200 205
  - Tyr Tyr Met Leu Asn Val Thr Ser Ala Gly Glu Asp Gly Ile Tyr Tyr 210 215 220
  - Glu Pro Cys Thr Ala Asn Cys Thr Gly Tyr Ala Ala Asn Val Phe Ala 225 230 235 240

Thr Asp Ser Asn Gly His Ile Pro Glu Gly Phe Ser Phe Asn Asn Trp
245 250 255

- Phe Leu Leu Ser Asn Asp Ser Thr Leu Leu His Gly Lys Val Val Ser 260 265 270
- Asn Gln Pro Leu Leu Val Asn Cys Leu Leu Ala Ile Pro Lys Ile Tyr 275 280 285
- Gly Leu Gly Gln Phe Phe Ser Phe Asn His Thr Met Asp Gly Val Cys 290 295 300
- Asn Gly Ala Ala Val Asp Arg Ala Pro Glu Ala Leu Arg Phe Asn Ile 305 310 315 320
- Asn Asp Thr Ser Val Ile Leu Ala Glu Gly Ser Ile Val Leu His Thr 325 330 335
- Ala Leu Gly Thr Asn Leu Ser Phe Val Cys Ser Asn Ser Ser Asp Pro-340 345 350
- His Leu Ala Ile Phe Ala Ile Pro Leu Gly Ala Thr Glu Val Pro Tyr 355 360 365
- Tyr Cys Phe Leu Lys Val Asp Thr Tyr Asn Ser Thr Val Tyr Lys Phe 370 380
- Leu Ala Val Leu Pro Ser Thr Val Arg Glu Ile Val Ile Thr Lys Tyr 385 390 395 400
- Gly Asp Val Tyr Val Asn Gly Phe Gly Tyr Leu His Leu Gly Leu Leu 405 410 415
- Asp Ala Val Thr Ile Tyr Phe Thr Gly His Gly Thr Asp Asp Val 420 425 430
- Ser Gly Phe Trp Thr Ile Ala Ser Thr Asn Phe Val Asp Ala Leu Ile 435 440 445
- Glu Val Gln Gly Thr Ser Ile Gln Arg Ile Leu Tyr Cys Asp Asp Pro 450 455 460
- Val Ser Gln Leu Lys Cys Ser Gln Val Ala Phe Asp Leu Asp Asp Gly
  465 470 475 480
- Phe Tyr Pro Ile Ser Ser Arg Asn Leu Leu Ser His Glu Gln Pro Ile

495

Ser	Phe	Val	Thr	Leu	Pro	Ser	Phe	Asn	Asp	His	Ser	Phe	Val	ne $A$	Ile
			500				2	505	. :				510		

Thr Val Ser Ala Ala Phe Gly Gly Leu Ser Ser Ala Asn Leu Val Ala 515 520 525

Ser Asp Thr Thr Ile Asn Gly Phe Ser Ser Phe Cys Val Asp Thr Arg 530 535 540

Gln Phe Thr Ile Thr Leu Phe Tyr Asn Val Thr Asn Ser Tyr Gly Tyr 545 550 555 560

Val Ser Lys Ser Gln Asp Ser Asn Cys Pro Phe Thr Leu Gln Ser Val 565 570 575

Asn Asp Tyr Leu Ser Phe Ser Lys Phe Cys Val Ser Thr Ser Leu Leu 580 585 590

Ala Gly Ala Cys Thr Ile Asp Leu Phe Gly Tyr Pro Ala Phe Gly Ser 595 600 605

Gly Val Lys Leu Thr Ser Leu Tyr Phe Gln Phe Thr Lys Gly Glu Leu 610 615 620

Ile Thr Gly Thr Pro Lys Pro Leu Glu Gly Ile Thr Asp Val Ser Phe 625 630 635 640

Met Thr Leu Asp Val Cys Thr Lys Tyr Thr Ile Tyr Gly Phe Lys Gly 645 650 655

Glu Gly Ile Ile Thr Leu Thr Asn Ser Ser Ile Leu Ala Gly Val Tyr 660 665 670

Tyr Thr Ser Asp Ser Gly Gln Leu Leu Ala Phe Lys Asn Val Thr Ser 675 680 685

Gly Ala Val Tyr Ser Val Thr Pro Cys Ser Phe Ser Glu Gln Ala Ala 690 695 700

Tyr Val Asn Asp Asp Ile Val Gly Val Ile Ser Ser Leu Ser Asn Ser 705 710 715 720

Thr Phe Asn Asn Thr Arg Glu Leu Pro Gly Phe Phe Tyr His Ser Asn 725 730 735

- Asp Gly Ser Asn Cys Thr Glu Pro Val Leu Val Tyr Ser Asn Ile Gly
  740 745 750
- Val Cys Lys Ser Gly Ser Ile Gly Tyr Val Pro Ser Gln Tyr Gly Gln
  755 760 765
- Val Lys Ile Ala Pro Thr Val Thr Gly Asn Ile Ser Ile Pro Thr Asn 770 775 780
- Phe Ser Met Ser Ile Arg Thr Glu Tyr Leu Gln Leu Tyr Asn Thr Pro 785 790 795 800
- Val Ser Val Asp Cys Ala Thr Tyr Val Cys Asn Gly Asn Ser Arg Cys 805 810 815
- Lys Gln Leu Leu Thr Gln Tyr Thr Ala Ala Cys Lys Thr Ile Glu Ser 820 825 830
- Ala Leu Gln Leu Ser Ala Arg Leu Glu Ser Val Glu Val Asn Ser Met. 835 840 845
- Leu Thr Ile Ser Glu Glu Ala Leu Gln Leu Ala Thr Ile Ser Ser Phe 850 855 860
- Asn Gly Asp Gly Tyr Asn Phe Thr Asn Val Leu Gly Ala Ser Val Tyr 865 870 875 880
- Asp Pro Ala Ser Gly Arg Val Val Gln Lys Arg Ser Val Ile Glu Asp 885 890 895
- Leu Leu Phe Asn Lys Val Val Thr Asn Gly Leu Gly Thr Val Asp Glu 900 905 910
- Asp Tyr Lys Arg Cys Ser Asn Gly Arg Ser Val Ala Asp Leu Val Cys 915 920 925
- Ala Gln Tyr Tyr Ser Gly Val Met Val Leu Pro Gly Val Val Asp Ala 930 935 940
- Glu Lys Leu His Met Tyr Ser Ala Ser Leu Ile Gly Gly Met Ala Leu 945 950 955 960
- Gly Gly Ile Thr Ala Ala Ala Leu Pro Phe Ser Tyr Ala Val Gln 965 970 975

Ala Arg Leu Asn Tyr Leu Ala Leu Gln Thr Asp Val Leu Gln Arg Asn 980 985 990

- Gln Gln Leu Leu Ala Glu Ser Phe Asn Ser Ala Ile Gly Asn Ile Thr 995 1000 1005
- Ser Ala Phe Glu Ser Val Lys Glu Ala Ile Ser Gln Thr Ser Lys 1010 1015 1020
- Gly Leu Asn Thr Val Ala His Ala Leu Thr Lys Val Gln Glu Val 1025 1030 1035
- Val Asn Ser Gln Gly Ser Ala Leu Asn Gln Leu Thr Val Gln Leu 1040 1045 1050
- Gln His Asn Phe Gln Ala Ile Ser Ser Ser Ile Asp Asp Ile Tyr 1055 1060 1065
- Ser Arg Leu Asp Ile Leu Leu Ala Asp Val Gln Val Asp Arg Leu 1070 1080
- Ile Thr Gly Arg Leu Ser Ala Leu Asn Ala Phe Val Ala Gln Thr 1085 1090 1095
- Leu Thr Lys Tyr Thr Glu Val Gln Ala Ser Arg Lys Leu Ala Gln 1100 1105 1110
- Gln Lys Val Asn Glu Cys Val Lys Ser Gln Ser Gln Arg Tyr Gly 1115 1120 1125
- Phe Cys Gly Gly Asp Gly Glu His Ile Phe Ser Leu Val Gln Ala 1130 1135 1140
- Ala Pro Gln Gly Leu Leu Phe Leu His Thr Val Leu Val Pro Gly 1145 1150 1155
- Asp Phe Val Asn Val Leu Ala Ile Ala Gly Leu Cys Val Asn Gly 1160 1165 1170
- Glu Ile Ala Leu Thr Leu Arg Glu Pro Gly Leu Val Leu Phe Thr 1175 1180 1185
- His Glu Leu Gln Thr Tyr Thr Ala Thr Glu Tyr Phe Val Ser Ser 1190 1195 1200

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Arg Arg Met Phe Glu Pro Arg Lys Pro Thr Val Ser Asp Phe Val 1205 1210 1215 Gln Ile Glu Ser Cys Val Val Thr Tyr Val Asn Leu Thr Ser Asp 1220 1225 1230 100 Gln Leu Pro Asp Val Ile Pro Asp Tyr Ile Asp Val Asn Lys Thr 1235 1240 1245 . Leu Asp Glu Ile Leu Ala Ser Leu Pro Asn Arg Thr Gly Pro Ser 1250 1255 1260 Leu Pro Leu Asp Val Phe Asn Ala Thr Tyr Leu Asn Leu Thr Gly 1265 1270 1275 Glu Ile Ala Asp Leu Glu Gln Arg Ser Glu Ser Leu Arg Asn Thr 1280 1285 1290 Thr Glu Glu Leu Arg Ser Leu Ile Asn Asn Ile Asn Asn Thr Leu 1295 1300 1305 Val Asp Leu Glu Trp Leu Asn Arg Val Glu Thr Tyr Ile Lys Trp 1310 1315 1320 Pro Trp Trp Val Trp Leu Ile Ile Val Ile Val Leu Ile Phe Val 1325 1330 1335 Val Ser Leu Leu Val Phe Cys Cys Ile Ser Thr Gly Cys Cys Gly 1340 1345 1350 Cys Cys Gly Cys Cys Gly Ala Cys Phe Ser Gly Cys Cys Arg Gly 1355 1360 1365 Pro Arg Leu Gln Pro Tyr Glu Ala Phe Glu Lys Val His Val Gln 1370 1375 <210> 60 <211> 1349 <212> PRT <213> porcine hemagglutinating encephalomyelitis virus <400> 60 Met Phe Phe Ile Leu Leu Ile Ser Leu Pro Ser Ala Phe Ala Val Ile

Gly Asp Leu Lys Cys Thr Thr Ser Leu Ile Asn Asp Val Asp Thr Gly

25

20

- Val Pro Ser Ile Ser Ser Glu Val Val Asp Val Thr Asn Gly Leu Gly
  35 40 45
- Thr Phe Tyr Val Leu Asp Arg Val Tyr Leu Asn Thr Thr Leu Leu Leu 50 55 60
- Asn Gly Tyr Tyr Pro Ile Ser Gly Ala Thr Phe Arg Asn Met Ala Leu 65 70 75 80
- Lys Gly Thr Arg Leu Leu Ser Thr Leu Trp Phe Lys Pro Pro Phe Leu 85 90 95
- Ser Pro Phe Asn Asp Gly Ile Phe Ala Lys Val Lys Asn Ser Arg Phe 100 105 110
- Ser Lys Asp Gly Val Ile Tyr Ser Glu Phe Pro Ala Ile Thr Ile Gly
  115 120 125
- Ser Thr Phe Val Asn Thr Ser Tyr Ser Ile Val Val Glu Pro His Thr 130 135 140
- Ser Leu Ile Asn Gly Asn Leu Gln Gly Leu Leu Gln Ile Ser Val Cys 145 . 150 155 160
- Gln Tyr Thr Met Cys Glu Tyr Pro His Thr Ile Cys His Pro Asn Leu 165 170 175
- Gly Asn Gln Arg Ile Glu Leu Trp His Tyr Asp Thr Asp Val Val Ser 180 185 190
- Cys Leu Tyr Arg Arg Asn Phe Thr Tyr Asp Val Asn Ala Asp Tyr Leu 195 200 205
- Tyr Phe His Phe Tyr Gln Glu Gly Gly Thr Phe Tyr Ala Tyr Phe Thr 210 215 220
- Asp Thr Gly Phe Val Thr Lys Phe Leu Phe Lys Leu Tyr Leu Gly Thr 225 230 235 240
- Val Leu Ser His Tyr Tyr Val Met Pro Leu Thr Cys Asn Ser Ala Leu 245 250 255
- Ser Leu Glu Tyr Trp Val Thr Pro Leu Thr Thr Arg Gln Phe Leu Leu 260 265 270

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Ala Phe Asp Gln Asp Gly Val Leu Tyr His Ala Val Asp Cys Ala Ser 275 280 285 Asp Phe Met Ser Glu Ile Met Cys Lys Thr Ser Ser Ile Thr Pro Pro Thr Gly Val Tyr Glu Leu Asn Gly Tyr Thr Val Gln Pro Val Ala Thr 310 Val Tyr Arg Arg Ile. Pro Asp Leu Pro Asn Cys Asp Ile Glu Ala Trp 325 330 335 Leu Asn Ser Lys Thr Val Ser Ser Pro Leu Asn Trp Glu Arg Lys Ile 345 Phe Ser Asn Cys Asn Phe Asn Met Gly Arg Leu Met Ser Phe Ile Gln 360 Ala Asp Ser Phe Gly Cys Asn Asn Ile Asp Ala Ser Arg Leu Tyr Gly . 380 Met Cys Phe Gly Ser Ile Thr Ile Asp Lys Phe Ala Ile Pro Asn Ser 385 390 395 400 Arg Lys Val Asp Leu Gln Val Gly Lys Ser Gly Tyr Leu Gln Ser Phe 405 410 Asn Tyr Lys Ile Asp Thr Ala Val Ser Ser Cys Gln Leu Tyr Tyr Ser 425 430 Leu Pro Ala Ala Asn Val Ser Val Thr His Tyr Asn Pro Ser Ser Trp 440 Asn Arg Arg Tyr Gly Phe Asn Asn Gln Ser Phe Gly Ser Arg Gly Leu 455 460 His Asp Ala Val Tyr Ser Gln Gln Cys Phe Asn Thr Pro Asn Thr Tyr 475 480 Cys Pro Cys Arg Thr Ser Gln Cys Ile Gly Gly Ala Gly Thr Gly Thr 490 Cys Pro Val Gly Thr Thr Val Arg Lys Cys Phe Ala Ala Val Thr Lys 500 505

Ala Thr Lys Cys Thr Cys Trp Cys Gln Pro Asp Pro Ser Thr Tyr Lys 515 520 525 Gly Val Asn Ala Trp Thr Cys Pro Gln Ser Lys Val Ser Ile Gln Pro 530 535 540 Gly Gln His Cys Pro Gly Leu Gly Leu Val Glu Asp Asp Cys |Ser Gly 555 560 Asn Pro Cys Thr Cys Lys Pro Gln Ala Phe Ile Gly Trp Ser Ser Glu 565. 570 575 Thr Cys Leu Gln Asn Gly Arg Cys Asn Ile Phe Ala Asn Phe Ile Leu 585 Asn Asp Val Asn Ser Gly Thr Thr Cys Ser Thr Asp Leu Gln Gln Gly 595 600 605 Asn Thr Ile Ile Thr Thr Asp Val Cys Val Asn Tyr Asp Leu Tyr Gly 615 620 Ile Thr Gly Gln Gly Ile Leu Ile Glu Val Asn Ala Thr Tyr Tyr Asn 630 635 640 Ser Trp Gln Asn Leu Leu Tyr Asp Ser Ser Gly Asn Leu Tyr Gly Phe 645 650 655 Arg Asp Tyr Leu Ser Asn Arg Thr Phe Leu Ile Arg Ser Cys Tyr Ser 660 665 670 Gly Arg Val Ser Ala Val Phe His Ala Asn Ser Ser Glu Pro Ala Leu 675 680 685 Met Phe Arg Asn Leu Lys Cys Ser His Val Phe Asn Asn Thr Ile Leu 690 695 . 700 Arg Gln Ile Gln Leu Val Asn Tyr Phe Asp Ser Tyr Leu Gly Cys Val 710 715 705 Val Asn Ala Tyr Asn Asn Thr Ala Ser Ala Val Ser Thr Cys Asp Leu 725 730 Thr Val Gly Ser Gly Tyr Cys Val Asp Tyr Val Thr Ala Leu Arg Ser

Arg Arg Ser Phe Thr Thr Gly Tyr Arg Phe Thr Asn Phe Glu Pro Phe

760

765

Ala Ala Asn Leu Val Asn Asp Ser Ile Glu Pro Val Gly Gly Leu Tyr
770 775 780

Glu Ile Gln Ile Pro Ser Glu Phe Thr Ile Gly Asn Leu Glu Glu Phe
785 790 795 800

Ile Gln Thr Arg Ser Pro Lys Val Thr Ile Asp Cys Ala Thr Phe Val 805 810 815

Cys Gly Asp Tyr Ala Ala Cys Arg Gln Gln Leu Ala Glu Tyr Gly Ser 820 825 830

Phe Cys Glu Asn Ile Asn Ala Ile Leu Thr Glu Val Asn Glu Leu Leu 835 840 845

Asp Thr Thr Gln Leu Gln Val Ala Asn Ser Leu Met Asn Gly Val Thr 850 855 860

Leu Ser Thr Lys Ile Lys Asp Gly Ile Asn Phe Asn Val Asp Asp Ile 865 870 880

Asn Phe Ser Pro Val Leu Gly Cys Leu Gly Ser Glu Cys Asn Arg Ala 885 890 895

Ser Thr Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp Lys Val Lys Leu 900 905 910

Ser Asp Val Gly Phe Val Gln Ala Tyr Asn Asn Cys Thr Gly Gly Ala 915 920 925

Glu Ile Arg Asp Leu Ile Cys Val Gln Ser Tyr Asn Gly Ile Lys Val 930 935 940

Leu Pro Pro Leu Leu Ser Glu Asn Gln Ile Ser Gly Tyr Thr Leu Ala 945 950 955 960

Ala Thr Ala Ala Ser Leu Phe Pro Pro Trp Thr Ala Ala Ala Gly Val 965 970 975

Pro Phe Tyr Leu Asn Val Gln Tyr Arg Ile Asn Gly Leu Gly Val Thr 980 985 990

Met Asp Val Leu Ser Gln Asn Gln Lys Leu Ile Ala Ser Ala Phe Asn 995 1005

Asn Ala Leu Asp Ala Ile Gln Glu Gly Phe Asp Ala Thr Asn Ser 1010 1015 1020

- Ala Leu Val Lys Ile Gln Ala Val Val Asn Ala Asn Ala Glu Ala 1025 1030 1035
- Leu Asn Asn Leu Leu Gln Gln Leu Ser Asn Arg Phe Gly Ala Ile 1040 1045 1050
- Ser Ala Ser Leu Gln Glu Ile Leu Ser Arg Leu Asp Ala Leu Glu 1055 1060 1065
- Ala Lys Ala Gln Ile Asp Arg Leu Ile Asn Gly Arg Leu Thr Ala 1070 1075 1080
- Leu Asn Ala Tyr Val Ser Gln Gln Leu Ser Asp Ser Thr Leu Val 1085 1090 1095
- Lys Phe Ser Ala Ala Gln Ala Ile Glu Lys Val Asn Glu Cys Val 1100 1105 1110
- Lys Ser Gln Ser Ser Arg Ile Asn Phe Cys Gly Asn Gly Asn His 1115 1120 1125
- Ile Ile Ser Leu Val Gln Asn. Ala Pro Tyr Gly Leu Tyr Phe Ile 1130 1135 1140
- His Phe Ser Tyr Val Pro Thr Lys Tyr Val Thr Ala Lys Val Ser 1145 1150 1155
- Pro Gly Leu Cys Ile Ala Gly Asp Ile Gly Ile Ser Pro Lys Ser 1160 1165 1170
- Gly Tyr Phe Ile Asn Val Asn Asn Ser Trp Met Phe Thr Gly Ser 1175 1180 1185
  - Ser Tyr Tyr Tyr Pro Glu Pro Ile Thr Gln Asn Asn Val Val Val 1190 1195 1200
  - Met Ser Thr Cys Ala Val Asn Tyr Thr Lys Ala Pro Asp Leu Met 1205 1210 1215
  - Leu Asn Thr Ser Thr Pro Asn Leu Pro Asp Phe Lys Glu Glu Leu 1220 1225 1230

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Tyr Gln Trp Phe Lys Asn Gln Ser Ser Val Ala Pro Asp Leu Ser 1235 1240 1245 Leu Asp Tyr Ile Asn Val Thr Phe Leu Asp Leu Gln Asp Glu Met 1250 1255 1260 Asn Arg Leu Gln Glu Ala Ile Lys Val Leu Asn Gln Ser Tyr Ile 1265 1270 1275 Asn Leu Lys Asp Ile Gly Thr Tyr Glu Tyr Tyr Val Lys Trp Pro 1280 1285 Trp Tyr Val Trp Leu Leu Ile Gly Leu Ala Gly Val Ala Met Leu 1295 1300 1305 Val Leu Leu Phe Phe Ile Cys Cys Cys Thr Gly Cys. Gly Thr Ser 1315 1320 Cys Phe Lys Lys Cys Gly Gly Cys Cys Asp Asp Tyr Thr Gly His 1325 1330 1335. Gln Glu Phe Val Ile Lys Thr Ser His Asp Asp 1340 1345 ٠. <210> 61 <211> 1225 <212> PRT <213> Porcine respiratory coronavirus <400> 61 Met Lys Lys Leu Phe Val Val Leu Val Val Met Pro Leu Ile Tyr Gly 5 10 15 Asp Lys Phe Pro Thr Ser Val Val Ser Asn Cys Thr Asp Gln Cys Ala Ser Tyr Val Ala Asn Val Phe Thr Thr Gln Pro Gly Gly Phe Ile Pro . . Ser Asp Phe Ser Phe Asn Asn Trp Phe Leu Leu Thr Asn Ser Ser Thr . 50 . 55

Leu Trp Pro Val Pro Ser Phe Glu Glu Ala Ala Ser Thr Phe Cys Phe

Leu Val Ser Gly Lys Leu Val Thr Lys Gln Pro Leu Leu Val Asn Cys

90

95

Glu Gly Ala Asp Phe Asp Gln Cys Asn Gly Ala Val Leu Asn Asn Thr 100 105 110

Val Asp Val Ile Arg Phe Asn Leu Asn Phe Thr Thr Asn Val Gln Ser 115 120 125

Gly Lys Gly Ala Thr Val Phe Ser Leu Asn Thr Thr Gly Gly Val Thr 130 135 140

Leu Glu Ile Ser Cys Tyr Asn Asp Thr Val Ser Asp Ser Ser Phe Ser 145 150 155 160

Ser Tyr Gly Glu Ile Pro Phe Gly Val Thr Asn Gly Pro Arg Tyr Cys 165 170 175

Tyr Val Leu Tyr Asn Gly Thr Ala Leu Lys Tyr Leu Gly Thr Leu Pro 180 185 190

Pro Ser Val Lys Glu Ile Ala Ile Ser Lys Trp Gly His Phe Tyr Ile 195 200 205

Asn Gly Tyr Asn Phe Phe Ser Thr Phe Pro Ile Asp Cys Ile Ser Phe 210 215 220

Asn Leu Thr Thr Gly Asp Ser Asp Val Phe Trp Thr Ile Ala Tyr Thr 225 230 235 240

Ser Tyr Thr Glu Ala Leu Val Gln Val Glu Asn Thr Ala 11e Thr Asn 245 250 255

Val Thr Tyr Cys Asn Ser Tyr Val Asn Asn Ile Lys Cys Ser Gln Leu 260 265 270

Thr Ala Asn Leu Asn Asn Gly Phe Tyr Pro Val Ser Ser Ser Glu Val 275 280 285

Gly Ser Val Asn Lys Ser Val Val Leu Pro Ser Phe Leu Thr His 290 295 300

Thr Ile Val Asn Ile Thr Ile Gly Leu Gly Met Lys Arg Ser Gly Tyr 305 310 315 320

Gly Gln Pro Ile Ala Ser Thr Leu Ser Asn Ile Thr Leu Pro Met Gln 325 330 335

- Asp Asn Asn Thr Asp Val Tyr Cys Val Arg Ser Asp Gln Phe Ser Val 340 345 350
- Tyr Val His Ser Thr Cys Lys Ser Ala Leu Trp Asp Asn Val Phe Lys 355
- Arg Asn Cys Thr Asp Val Leu Asp Ala Thr Ala Val Ile Lys Thr Gly 370 375 380
- Thr Cys Pro Phe Ser Phe Asp Lys Leu Asn Asn Tyr Leu Thr Phe Asn 385 . 390 395 400
- Lys Phe Cys Leu Ser Leu Ser Pro Val Gly Ala Asn Cys Lys Phe Asp 405 410 415
- Val Ala Ala Arg Thr Arg Thr Asn Glu Gln Val Val Arg Ser Leu Tyr
  420 425 430
- Val Ile Tyr Glu Glu Gly Asp Ser Ile Val Gly Val Pro Ser Asp Asn.
  435 440 445
- Ser Gly Leu His Asp Leu Ser Val Leu His Leu Asp Ser Cys Thr Asp 450 450
- Tyr Asn Ile Tyr Gly Arg Thr Gly Val Gly Ile Ile Arg GIn Thr Asn 465 470 475 480
- Arg Thr Leu Leu Ser Gly Leu Tyr Tyr Thr Ser Leu Ser Gly Asp Leu 485 490 495
- Leu Gly Phe Lys Asn Val Ser Asp Gly Val Ile Tyr Ser Val Thr Pro 500 510
- Cys Asp Val Ser Ala Gln Ala Ala Val Ile Asp Gly Thr Ile Val Gly 515 520 525
- Ala Ile Thr Ser Ile Asn Ser Glu Leu Leu Gly Leu Thr His Trp Thr 530 540
- Ile Thr Pro Asn Phe Tyr Tyr Tyr Ser Ile Tyr Asn Tyr Thr Asn Asp 545 550 555 560
- Lys Thr Arg Gly Thr Pro Ile Asp Ser Asn Asp Val Gly Cys Glu Pro 565 570 575

Val Ile Thr Tyr Ser Asn Ile Gly Val Cys Lys Asn Gly Ala Leu Val 580 585 590

- Phe Ile Asn Val Thr His Ser Asp Gly Asp Val Gln Pro Ile Ser Thr 595 600 605
- Gly Asn Val Thr Ile Pro Thr Asn Phe Thr Ile Ser Val Gln Val Glu 610 615 620
- Tyr Ile Gln Val Tyr Thr Thr Pro Val Ser Ile Asp Cys Ser Arg Tyr 625 630 635 640
- Val Cys Asn Gly Asn Pro Arg Cys Asn Lys Leu Leu Thr Gln Tyr Val 645 650 655
- Ser Ala Cys Gln Thr Ile Glu Gln Ala Leu Ala Met Gly Ala Arg Leu 660 665 670
- Glu Asn Met Glu Val Asp Ser Met Leu Phe Val Ser Glu Asn Ala Leu 675 680 685
- Lys Leu Ala Ser Val Glu Ala Phe Asn Ser Ser Glu Thr Leu Asp Pro 690 695 700
- Ile Tyr Thr Gln Trp Pro Asn Ile Gly Gly Phe Trp Leu Glu Gly Leu 705 710 715 720
- Lys Tyr Ile Leu Pro Ser Asp Asn Ser Lys Arg Lys Tyr Arg Ser Ala 725 730 735
- Ile Glu Asp Leu Leu Phe Ser Lys Val Val Thr Ser Gly Leu Gly Thr
  740 745 750
- Val Asp Glu Asp Tyr Lys Arg Cys Thr Gly Gly Tyr Asp Ile Ala Asp
  755 760 765
- Leu Val Cys Ala Gln Tyr Tyr Asn Gly Ile Met Val Leu Pro Gly Val 770 780
- Ala Asn Ala Asp Lys Met Thr Met Tyr Thr Ala Ser Leu Ala Gly Gly 785 790 795 800
- Ile Thr Leu Gly Ala Phe Gly Gly Gly Ala Val Ser Ile Pro Phe Ala 805 810 815

Val Ala Val Gln Ala Arg Leu Asn Tyr Val Ala Leu Gln Thr Asp Val 820 825 830

- Leu Asn Lys Asn Gln Gln Ile Leu Ala Ser Ala Phe Asn Gln Ala Ile 835 840 845
- Gly Asn Ile Thr Gln Ser Phe Gly Lys Val Asn Asp Ala Ile His Gln 850 855 860
- Thr Ser Arg Gly Leu Thr Thr Val Ala Lys Ala Leu Ala Lys Val Gln 865 870 875 880
- Asp Val Val Asn Thr Gln Gly Gln Ala Leu Arg His Leu Thr Val Gln 885 890 895
- Leu Gln Asn Asn Phe Gln Ala Ile Ser Ser Ser Ile Ser Asp Ile Tyr 900 905 910
- Asn Arg Leu Asp Glu Leu Ser Ala Asp Ala Gln Val Asp Arg Leu Ile 915 920 925
- Thr Gly Arg Leu Thr Ala Leu Asn Ala Phe Val Ser Gln Thr Leu Thr 930 935 940
- Arg Gln Ala Glu Val Arg Ala Ser Arg Gln Leu Ala Lys Asp Lys Val 945 950 955 960
- Asn Glu Cys Val Arg Ser Gln Ser Gln Arg Phe Gly Phe Cys Gly Asn 965 970 975
- Gly Thr His Leu Phe Ser Leu Ala Asn Ala Ala Pro Asn Gly Met Ile 980 985 990
- Phe Phe His Thr Val Leu Leu Pro Thr Ala Tyr Glu Thr Val Thr Ala 995 1000 1005
- Trp Ser Gly Ile Cys Ala Leu Asp Gly Asp Arg Thr Phe Gly Leu 1010 1015 1020
- Val Val Lys Asp Val Gln Leu Thr Leu Phe Arg Asn Leu Asp Asp 1025 1030 1035
- Lys Phe Tyr Leu Thr Pro Arg Thr Met Tyr Gln Pro Arg Val Ala 1040 1045 1050
- Thr Ser Ser Asp Phe Val Gln Ile Glu Gly Cys Asp Val Leu Phe

1065

Val Asn Thr Thr Val Ser Asp Leu Pro Ser Ile Ile Pro Asp Tyr 1070 1075 1080

1060

Ile Asp Ile Asn Gln Thr Val Gln Asp Ile Leu Glu Asn Phe Arg 1085 1090 1095

Pro Asn Trp Thr Val Pro Glu Leu Thr Leu Asp Val Phe Asn Ala 1100 1105 1110

Thr Tyr Leu Asn Leu Thr Gly Glu Ile Asp Asp Leu Glu Phe Arg. 1115 1120 1125

Ser Glu Lys Leu His Asn Thr Thr Val Glu Leu Ala Ile Leu Ile 1130 1135 1140

Asp Asn Ile Asn Asn Thr Leu Val Asn Leu Glu Trp Leu Asn Arg 1145 1150 1155

Ile Glu Thr Tyr Val Lys Trp Pro Trp Tyr Val Trp Leu Leu Ile 1160 1165 1170

Gly Leu Val Val Ile Phe Cys Ile Pro Leu Leu Phe Cys Cys 1175 1180 1185

Cys Ser Thr Gly Cys Cys Gly Cys Ile Gly Cys Leu Gly Ser Cys 1190 1195 1200

Cys His Ser Ile Phe Ser Arg Arg Gln Phe Glu Asn Tyr Glu Pro 1205 1210 1215

Ile Glu Lys Val His Val His 1220 1225

<210> 62

·<211> 82

-212\ DDT

<213> Porcine transmissible gastroenteritis.coronoavirus

<400> 62

Met Thr Phe Pro Arg Ala Leu Thr Val Ile Asp Asp Asn Gly Met Val 1 5 10 15

Ile Asn Ile Ile Phe Trp Phe Leu Leu Ile Ile Leu Ile Leu Leu 20 25 30

Ser Ile Ala Leu Leu Asn Ile Ile Lys Leu Cys Met Val Cys Cys Asn 35 40 .45

Leu Gly Arg Thr Val Ile Ile Val Pro Ala Gln His Ala Tyr Asp Ala 50 60

Tyr Lys Asn Phe Met Arg Ile Lys Ala Tyr Asn Pro Asp Gly Ala Leu 65 70 75 80

Leu Ala

<210> 63

<211> 4376

<212> PRT

<213> Severe acute respiratory syndrome virus

<400> 63

Met Glu Ser Leu Val Leu Gly Val Asn Glu Lys Thr His Val Gln Leu 1 5 10 15

Ser Leu Pro Val Leu Gln Val Arg Asp Val Leu Val Arg Gly Phe Gly 20 25 30

Asp Ser Val Glu Glu Ala Leu Ser Glu Ala Arg Glu His Leu Lys Asn 35 40 45

Gly Thr Cys Gly Leu Val Glu Leu Glu Lys Gly Val Leu Pro Gln Leu 50 55 60

Glu Gln Pro Tyr Val Phe Ile Lys Arg Ser Asp Ala Leu Ser Thr Asn 65 70 75 80

His Gly His Lys Val Val Glu Leu Val Ala Glu Met Asp Gly Ile Gln 85 90 95

Tyr Gly Arg Ser Gly Ile Thr Leu Gly Val Leu Val Pro His Val Gly 100 105

Glu Thr Pro Ile Ala Tyr Arg Asn Val Leu Leu Arg Lys Asn Gly Asn 115 120 . 125

Lys Gly Ala Gly Gly His Ser Tyr Gly Ile Asp Leu Lys Ser Tyr Asp 130 135 140

Leu Gly Asp Glu Leu Gly Thr Asp Pro Ile Glu Asp Tyr Glu Gln Asn

150

155

160

Trp Asn Thr Lys His Gly Ser Gly Ala Leu Arg Glu Leu Thr Arg Glu.
165 170 175

Leu Asn Gly Gly Ala Val Thr Arg Tyr Val Asp Asn Asn Phe Cys Gly
180 185 190

Pro Asp Gly Tyr Pro Leu Asp Cys Ile Lys Asp Phe Leu Ala Arg Ala 195 200 205

Gly Lys Ser Met Cys Thr Leu Ser Glu Gln Leu Asp Tyr Ile Glu Ser 210 220

Lys Arg Gly Val Tyr Cys Cys Arg Asp His Glu His Glu Ile Ala Trp 225 230 235 240

Phe Thr Glu Arg Ser Asp Lys Ser Tyr Glu His Gln Thr Pro Phe Glu 245 250 255

Ile Lys Ser Ala Lys Lys Phe Asp Thr Phe Lys Gly Glu Cys Pro Lys 260 265 270

Phe Val Phe Pro Leu Asn Ser Lys Val Lys Val Ile Gln Pro Arg Val 275 280 285

Glu Lys Lys Thr Glu Gly Phe Met Gly Arg Ile Arg Ser Val Tyr 290 295 300

Pro Val Ala Ser Pro Gln Glu Cys Asn Asn Met His Leu Ser Thr Leu 305 310 315 320

Met Lys Cys Asn His Cys Asp Glu Val Ser Trp Gln Thr Cys Asp Phe 325 330 335

Leu Lys Ala Thr Cys Glu His Cys Gly Thr Glu Asn Leu Val Ile Glu 340 345 350

Gly Pro Thr Thr Cys Gly Tyr Leu Pro Thr Asn Ala Val Val Lys Met 355 360 365

Pro Cys Pro Ala Cys Gln Asp Pro Glu Ile Gly Pro Glu His Ser Val 370 375 380

Ala Asp Tyr His Asn His Ser Asn Ile Glu Thr Arg Leu Arg Lys Gly 385 390 395 400

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Gly Arg Thr Arg Cys Phe Gly Gly Cys Val Phe Ala Tyr Val Gly Cys 405 410 415

- Tyr Asn Lys Arg Ala Tyr Trp Val Pro Arg Ala Ser Ala Asp Ile Gly 420' 425 430
- Ser Gly His Thr Gly Ile Thr Gly Asp Asn Val Glu Thr Leu Asn Glu 435 440 445
- Asp Leu Leu Glu Ile Leu Ser Arg Glu Arg Val Asn Ile Asn Ile Val 450 455 460
- Gly Asp Phe His Leu Asn Glu Glu Val Ala Ile Ile Leu Ala Ser Phe 465 470 475 480
- Ser Ala Ser Thr Ser Ala Phe Ile Asp Thr Ile Lys Ser Leu Asp Tyr 485 490 495
- Lys Ser Phe Lys Thr Ile Val Glu Ser Cys Gly Asn Tyr Lys Val Thr 500 505 510
- Lys Gly Lys Pro Val Lys Gly Ala Trp Asn Ile Gly Gln Gln Arg Ser 515 520 525
- Val Leu Thr Pro Leu Cys Gly Phe Pro Ser Gln Ala Ala Gly Val Ile 530 535 540
- Arg Ser Ile Phe Ala Arg Thr Leu Asp Ala Ala Asn His Ser Ile Pro 545 550 555 560
- Asp Leu Gln Arg Ala Ala Val Thr Ile Leu Asp Gly Ile Ser Glu Gln 565 570 575
- Ser Leu Arg Leu Val Asp Ala Met Val Tyr Thr Ser Asp Leu Leu Thr 580 585 590
- Asn Ser Val Ile Ile Met Ala Tyr Val Thr Gly Gly Leu Val Gln Gln 595 600 605
- Thr Ser Gln Trp Leu Ser Asn Leu Leu Gly Thr Thr Val Glu Lys Leu 610 615 620
- Arg Pro Ile Phe Glu Trp Ile Glu Ala Lys Leu Ser Ala Gly Val Glu 625 635 640

Phe Leu Lys Asp Ala Trp Glu Ile Leu Lys Phe Leu Ile Thr Gly Val 645 650 655

- Phe Asp Ile Val Lys Gly Gln Ile Gln Val Ala Ser Asp Asn Ile Lys 660 665 670
- Asp Cys Val Lys Cys Phe Ile Asp Val Val Asn Lys Ala Leu Glu Met 675 680 685
- Cys Ile Asp Gln Val Thr Ile Ala Gly Ala Lys Leu Arg Ser Leu Asn 690 695 700.
- Leu Gly Glu Val Phe Ile Ala Gln Ser Lys Gly Leu Tyr Arg Gln Cys 705 710 715 720
- Ile Arg Gly Lys Glu Gln Leu Gln Leu Leu Met Pro Leu Lys Ala Pro 725 730 735
- Lys Glu Val Thr Phe Leu Glu Gly Asp Ser His Asp Thr Val Leu Thr 740 745 750
- Ser Glu Glu Val Val Leu Lys Asn Gly Glu Leu Glu Ala Leu Glu Thr
  755 760 765
- Pro Val Asp Ser Phe Thr Asn Gly Ala Ile Val Gly Thr Pro Val Cys
  770 775 780
- Val Asn Gly Leu Met Leu Leu Glu Ile Lys Asp Lys Glu Gln Tyr Cys 785 790 795 800
- Ala Leu Ser Pro Gly Leu Leu Ala Thr Asn Asn Val Phe Arg Leu Lys 805 810 815
- Gly Gly Ala Pro Ile Lys Gly Val Thr Phe Gly Glu Asp Thr Val Trp 820 825 830
- Glu Val Gln Gly Tyr Lys Asn Val Arg Ile Thr Phe Glu Leu Asp Glu 835 840 845
- Arg Val Asp Lys Val Leu Asn Glu Lys Cys Ser Val Tyr Thr Val Glu 850 855 860
- Ser Gly Thr Glu Val Thr Glu Phe Ala Cys Val Val Ala Glu Ala Val 865 870 875 880

Val Lys Thr Leu Gln Pro Val Ser Asp Leu Leu Thr Asn Met Gly Ile 885 890 895

- Asp Leu Asp Glu Trp Ser Val Ala Thr Phe Tyr Leu Phe Asp Asp Ala 900 905 910
- Gly Glu Glu Asn Phe Ser Ser Arg Met Tyr Cys Ser Phe Tyr Pro Pro 915 920 925
- Asp Glu Glu Glu Glu Asp Asp Ala Glu Cys Glu Glu Glu Glu Ile Asp 930 935 940
- Glu Thr Cys Glu His Glu Tyr Gly Thr Glu Asp Asp Tyr Gln Gly Leu 945 950 955 960
- Pro Leu Glu Phe Gly Ala Ser Ala Glu Thr Val Arg Val Glu Glu 965 970 975
- Glu Glu Glu Asp Trp Leu Asp Asp Thr Thr Glu Gln Ser Glu Ile Glu 980 985 990
- Pro Glu Pro Glu Pro Thr Pro Glu Glu Pro Val Asn Gln Phe Thr Gly 995 1000 1005
- Tyr Leu Lys Leu Thr Asp Asn Val Ala Ile Lys Cys Val Asp Ile 1010 1015 1020
- Val Lys Glu Ala Gln Ser Ala Asn Pro Met Val Ile Val Asn Ala 1025 1030 1035
- Ala Asn Ile His Leu Lys His Gly Gly Gly Val Ala Gly Ala Leu 1040 1045 1050
- Asn Lys Ala Thr Asn Gly Ala Met Gln Lys Glu Ser Asp Asp Tyr 1055 1060 1065
- Ile Lys Leu Asn Gly Pro Leu Thr Val Gly Gly Ser Cys Leu Leu 1070 1080
- Ser Gly His Asn Leu Ala Lys Lys Cys Leu His Val Val Gly Pro 1085 1090 1095
- Asn Leu Asn Ala Gly Glu Asp Ile Gln Leu Leu Lys Ala Ala Tyr 1100 1105 1110
- Glu Asn Phe Asn Ser Gln Asp Ile Leu Leu Ala Pro Leu Leu Ser

1120

1125

- Ala Gly Ile Phe Gly Ala Lys Pro Leu Gln Ser Leu Gln Val Cys . 1130 1135 1140
- Val Gln Thr Val Arg Thr Gln Val Tyr Ile Ala Val Asn Asp Lys 1145 1150 1155
- Ala Leu Tyr Glu Gln Val Val Met Asp Tyr Leu Asp Asn Leu Lys 1160 1165 1170
- Pro Arg Val Glu Ala Pro Lys Gln Glu Glu Pro Pro Asn Thr Glu 1175 1180 1185
- Asp Ser Lys Thr Glu Glu Lys Ser Val Val Gln Lys Pro Val Asp 1190 1195 1200
- Val Lys Pro Lys Ile Lys Ala Cys Ile Asp Glu Val Thr Thr Thr 1205 1210 1215
- Leu Glu Glu Thr Lys Phe Leu Thr Asn Lys Leu Leu Phe Ala 1220 1225 1230
- Asp lie Asn Gly Lys Leu Tyr His Asp Ser Gln Asn Met Leu Arg 1235 1240 1245
- Gly Glu Asp Met Ser Phe Leu Glu Lys Asp Ala Pro Tyr Met Val 1250 1255 1260
- Gly Asp Val Ile Thr Ser Gly Asp Ile Thr Cys Val Val Ile Pro 1265 1270 1275
- Ser Lys Lys Ala Gly Gly Thr Thr Glu Met Leu Ser Arg Ala Leu 1280 1285 1290
- Lys Lys Val Pro Val Asp Glu Tyr Ile Thr Thr Tyr Pro Gly Gln 1295 1300 1305
- Gly Cys Ala Gly Tyr Thr Leu Glu Glu Ala Lys Thr Ala Leu Lys 1310 1315 1320
- Lys Cys Lys Ser Ala Phe Tyr Val Leu Pro Ser Glu Ala Pro Asn 1325 1330 1335
- Ala Lys Glu Glu Ile Leu Gly Thr Val Ser Trp Asn Leu Arg Glu. 1340 1350

Met Leu Ala His Ala Glu Glu Thr Arg Lys Leu Met Pro Ile Cys 1355 1360 1365

- Met Asp Val Arg Ala Ile Met Ala Thr Ile Gln Arg Lys Tyr Lys 1370 1375 1380
- Gly Ile Lys Ile Gln Glu Gly Ile Val Asp Tyr Gly Val Arg Phe 1385 1390 1395
- Phe Phe Tyr Thr Ser Lys Glu Pro Val Ala Ser Ile Ile Thr Lys 1400 1405 1410
- Leu Asn Ser Leu Asn Glu Pro Leu Val Thr Met Pro Ile Gly Tyr 1415 1420 1425
- Val Thr His Gl'y Phe Asn Leu Glu Glu Ala Ala Arg Cys Met Arg 1430 1435 1440
- Ser Leu Lys Ala Pro Ala Val Val Ser Val Ser Ser Pro Asp Ala 1445 1450 1455
- Val Thr Thr Tyr Asn Gly Tyr Leu Thr Ser Ser Ser Lys Thr Ser 1460 1465 1470
- Glu Glu His Phe Val Glu Thr Val Ser Leu Ala Gly Ser Tyr Arg 1475 1480 1485
- Asp Trp Ser Tyr Ser Gly Gln Arg Thr Glu Leu Gly Val Glu Phe 1490 1495 1500
- Leu Lys Arg Gly Asp Lys Ile Val Tyr His Thr Leu Glu Ser Pro 1505 1510 1515
- Val Glu Phe His Leu Asp Gly Glu Val Leu Ser Leu Asp Lys Leu 1520 1525 1530
- Lys Ser Leu Leu Ser Leu Arg Glu Val Lys Thr Ile Lys Val Phe 1535 1540 1545
- Thr Thr Val Asp Asn Thr Asn Leu His Thr Gln Leu Val Asp Met 1550 1560
- Ser Met Thr Tyr Gly Gln Gln Phe Gly Pro Thr Tyr Leu Asp Gly 1565 1570 1575

- Ala Asp Val Thr Lys Ile Lys Pro His Val Asn His Glu Gly Lys 1580 1585 1590
  - Thr Phe Phe Val Leu Pro Ser Asp Asp Thr Leu Arg Ser Glu Ala 1595 1600 1605
  - Phe Glu Tyr Tyr His Thr Leu Asp Glu Ser Phe Leu Gly Arg Tyr 1610 1615 1620
  - Met Ser Ala Leu Asn His Thr Lys Lys Trp Lys Phe Pro Gln Val 1625 1630 1635
  - Gly Gly Leu Thr Ser Ile Lys Trp Ala Asp Asn Asn Cys Tyr Leu 1640 1645 1650
  - Ser Ser Val Leu Leu Ala Leu Gln Gln Leu Glu Val. Lys Phe Asn 1655 1660 1665
  - Ala Pro Ala Leu Gln Glu Ala Tyr Tyr Arg Ala Arg Ala Gly Asp 1670 1675 1680
  - Ala Ala Asn Phe Cys Ala Leu Ile Leu Ala Tyr Ser Asn Lys Thr 1685 1690 1695
  - Val Gly Glu Leu Gly Asp Val Arg Glu Thr Met Thr His Leu Leu 1700 1705 1710
  - Gln His Ala Asn Leu Glu Ser Ala Lys Arg Val Leu Asn Val Val 1715 1720 1725
  - Cys Lys His Cys Gly Gln Lys Thr Thr Thr Leu Thr Gly Val Glu 1730 1735 1740
  - Ala Val Met Tyr Met Gly Thr Leu Ser Tyr Asp Asn Leu Lys Thr 1745 1750 1755
  - Gly Val Ser Ile Pro Cys Val Cys Gly Arg Asp Ala Thr Gln Tyr 1760 1765 1770
  - Leu Val Gln Gln Glu Ser Ser Phe Val Met Met Ser Ala Pro Pro 1775 1780 1785
  - Ala Glu Tyr Lys Leu Gln Gln Gly Thr Phe Leu Cys Ala Asn Glu 1790 1795 1800

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Tyr Thr Gly Asn Tyr Gln Cys Gly His Tyr Thr His Ile Thr Ala 1805 1810 1815

Lys Glu Thr Leu Tyr Arg Ile Asp Gly Ala His Leu Thr Lys Met 1820 1825 1830

i i i

- Ser Glu Tyr Lys Gly Pro Val Thr Asp Val Phe Tyr Lys Glu Thr 1835 1840 1845
- Ser Tyr Thr Thr Thr Ile Lys Pro Val Ser Tyr Lys Leu Asp Gly 1850 1855 1860
- Val Thr Tyr Thr Glu Ile Glu Pro Lys Leu Asp Gly Tyr Tyr Lys 1865 1870 1875
- Lys Asp Asn Ala Tyr Tyr Thr Glu Gln Pro Ile Asp Leu Val Pro 1880 1885 1890
- Thr Gln Pro Leu Pro Asn Ala Ser Phe Asp Asn Phe Lys Leu Thr 1895 1900 1905
- Cys Ser Asn Thr Lys Phe Ala Asp Asp Leu Asn Gln Met Thr Gly 1910 1915 1920
- Phe Thr Lys Pro Ala Ser Arg Glu Leu Ser Val Thr Phe Phe Pro 1925 1930 1935
- Asp Leu Asn Gly Asp Val Val Ala Ile Asp Tyr Arg His Tyr Ser 1940 1945 1950
- Ala Ser Phe Lys Lys Gly Ala Lys Leu Leu His Lys Pro Ile Val 1955 1960 1965
- Trp His Ile Asn Gln Ala Thr Thr Lys Thr Thr Phe Lys Pro Asn 1970 1975 1980
- Thr Trp Cys Leu Arg Cys Leu Trp Ser Thr Lys Pro Val Asp Thr 1985 1990 1995
- Ser Asn Ser Phe Glu Val Leu Ala Val Glu Asp Thr Gln Gly Met 2000 2005 2010
- Asp Asn Leu Ala Cys Glu Ser Gln Gln Pro Thr Ser Glu Glu Val 2015 2020 2025
- Val Glu Asn Pro Thr Ile Gln Lys Glu Val Ile Glu Cys Asp Val

.2030

2035

2040

- Lys Thr Thr Glu Val Val Gly Asn Val Ile Leu Lys Pro Ser Asp . 2045 2050 2055
- Glu Gly Val Lys Val Thr Gln Glu Leu Gly His Glu Asp Leu Met 2060 2065 2070
- Ala Ala Tyr Val Glu Asn Thr Ser Ile Thr Ile Lys Lys Pro Asn 2075 2080 2085
- Glu Leu Ser Leu Ala Leu Gly Leu Lys Thr Ile Ala Thr His Gly 2090 2095 2100
- Ile Ala Ala Ile Asn Ser Val Pro Trp Ser Lys Ile Leu Ala Tyr 2105 2110 2115
- Val Lys Pro Phe Leu Gly Gln Ala Ala Ile Thr Thr Ser Asn Cys 2120 2125 2130
- Ala Lys Arg Leu Ala Gln Arg Val Phe Asn Asn Tyr Met Pro Tyr 2135 2140 2145
- Val Phe Thr Leu Leu Phe Gln Leu Cys Thr Phe Thr Lys Ser Thr 2150 2155 2160
- Asn Ser Arg Ile Arg Ala Ser Leu Pro Thr Thr Ile Ala Lys Asn 2165 2170 2175
- Ser Val Lys Ser Val Ala Lys Leu Cys Leu Asp Ala Gly Ile Asn 2180 2185 2190
- Tyr Val Lys Ser Pro Lys Phe Ser Lys Leu Phe Thr Ile Ala Met 2195 2200 2205
- Trp Leu Leu Leu Ser Ile Cys Leu Gly Ser Leu Ile Cys Val 2210 2215 2220
- Thr Ala Ala Phe Gly Val Leu Leu Ser Asn Phe Gly Ala Pro Ser 2225 2230 2235
- Tyr Cys Asn Gly Val Arg Glu Leu Tyr Leu Asn Ser Ser Asn Val 2240 2245 2250
- Thr Thr Met Asp Phe Cys Glu Gly Ser Phe Pro Cys Ser Ile Cys 2255 2260 2265

						•								•
Leu	Ser 2270	Gly	Leu	Asp	Ser.	Leu 2275	Asp	Ser	Tyr		Ala 2280	Leu	Glu	Thr
Ile	Gln 2285		Thr	Ile		Ser 2290	Tyr	Lys	Leu	Asp	Leu 2295	Thr	Ile	Leu
Gly	Leu 2300	Ala	Ala	Glu	Trp	Val 2305	Leu	Ala	Tyr	Met	Leu 2310		Thr	Lys
Phe	Phe 2315	Tyr	Leu	Leu	Gly	Leu 2320	Ser	Ala	Ile	Met	Gln 2325		Phe	Phe
Gly	Tyr 2330		Ala	Ser	His	Phe 2335	Ile	Ser	Asn	Ser	Trp 2340	Leu	Met	Trp
Phe	Ile 2345		Ser	Iļė.	Val	Gln 2350	Met	Ala	Pro	Val	Ser 2355	Ala	Met	Val
Arg	Met 2360		Iļe	Phe	Phe	Ala 2365	Ser	Phe	Tyr		Ile 2370	Trp	Lys	Ser
Tyr	Val 2375		Ile	·Met	Asp	Gly 2380		Thr	Ser	Ser	Thr 2385		Met	Met
Cys	Tyr 2390		Arg	Asn	Arg	Ala 2395	Thr	Arg	Val	Glu	Cys 2400		Thr	lle
Val	Asn 2405		Met	Lys	Arg	Ser 2410		Tyr	Val	Tyr	Ala 2415		Gly	Gly
Arg	Gly 2420		ĊЛа	Гўз		His .2425		Trp	Asn	Cys	Leu 2430		Cys	Asp
Thr	Phe 2435		Thr	Gly	Ser	Thr 2440		Ile	Śer	Asp	Glu 2445		Ala	Arg
Asp	Leu 2450		Leu	Gln	. Phe	Lys 2455	_	Pro	Ile	Asn	Pro 2460		Asp	Gln
Ser	Ser 2465		: Ile	· Val	Asp	Ser 2470		Ala	Val	. Lys	Asn 2475		/ Ala	Leu
His	Leu 2480		Phe	Asp	Lys	Ala 2485		Gln	Lys	Thr	Tyr 2490		Arç	, His

Pro Leu Ser His Phe Val Asn Leu Asp Asn Leu Arg Ala Asn Asn 2495 2500 2505

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- Thr Lys Gly Ser Leu Pro Ile Asn Val Ile Val Phe Asp Gly Lys 2510 2515 2520
- Ser Lys Cys Asp Glu Ser Ala Ser Lys Ser Ala Ser Val Tyr Tyr 2525 2530 2535
- Ser Gln Leu Met Cys Gln Pro Ile Leu Leu Leu Asp Gln Ala Leu 2540 2550
- Val Ser Asp Val Gly Asp Ser Thr Glu Val Ser Val Lys Met Phe 2555 2560 2565
- Asp Ala Tyr Val Asp Thr Phe Ser Ala Thr Phe Ser Val Pro Met 2570 2575 2580
- Glu Lys Leu Lys Ala Leu Val Ala Thr Ala His Ser Glu Leu Ala 2585 2590 2595
- Lys Gly Val Ala Leu Asp Gly Val Leu Ser Thr Phe Val Ser Ala 2600 2605
- Ala Arg Gln Gly Val Val Asp Thr Asp Val Asp Thr Lys Asp Val 2615 2620 2625
- Ile Glu Cys Leu Lys Leu Ser His His Ser Asp Leu Glu Val Thr 2630 2635 2640
  - Gly Asp Ser Cys Asn Asn Phe Met Leu Thr Tyr Asn Lys Val Glu 2645 2650 2655
  - Asn Met Thr Pro Arg Asp Leu Gly Ala Cys Ile Asp Cys Asn Ala 2660 2665 2670
  - Arg His Ile Asn Ala Gln Val Ala Lys Ser His Asn Val Ser Leu 2675 2680 2685
  - Ile Trp Asn Val Lys Asp Tyr Met Ser Leu Ser Glu Gln Leu Arg 2690 2695 2700
  - Lys Gln Ile Arg Ser Ala Ala Lys Lys Asn Asn Ile Pro Phe Arg 2705 2710 2715

Leu Thr Cys Ala Thr Thr Arg Gln Val Val Asn Val Ile Thr Thr 2720 2725 2730

- Lys Ile Ser Leu Lys Gly Gly Lys Ile Val Ser Thr Cys Phe Lys 2735 2740 2745
- Leu Met Leu Lys Ala Thr Leu Leu Cys Val Leu Ala Ala Leu Val 2750 2755 2760
- Cys Tyr Ile Val Met Pro Val His Thr Leu Ser Ile His Asp Gly 2765 2770 2775
- Tyr Thr Asn Glu Ile Ile Gly Tyr Lys Ala Ile Gln Asp Gly Val 2780 2785 2790
- Thr Arg Asp Ile Ile Ser Thr Asp Asp Cys Phe Ala Asn Lys His 2795 2800 2805
- Ala Gly Phe Asp Ala Trp Phe Ser Gln Arg Gly Gly Ser Tyr Lys 2810 2815 2820
- Asn Asp Lys Ser Cys Pro Val Val Ala Ala Ile Ile Thr Arg Glu 2825 2830 2835
- Ile Gly Phe Ile Val Pro Gly Leu Pro Gly Thr Val Leu Arg Ala 2840 2845 2850
- Ile Asn Gly Asp Phe Leu His Phe Leu Pro Arg Val Phe Ser Ala 2855 2860 2865
- Val Gly Asn Ile Cys Tyr Thr Pro Ser Lys Leu Ile Glu Tyr Ser 2870 2875 2880
- Asp Phe Ala Thr Ser Ala Cys Val Leu Ala Ala Glu Cys Thr Ile 2885 2890 2895
- Phe Lys Asp Ala Met Gly Lys Pro Val Pro Tyr Cys Tyr Asp Thr 2900 2905 2910
- Asn Leu Clu Glu Gly Ser Ile Ser Tyr Ser Glu Leu Arg Pro Asp 2915 2920 2925
- Thr Arg Tyr Val Leu Met Asp Gly Ser Ile Ile Gln Phe Pro Asn 2930 2935 2940
- Thr Tyr Leu Glu Gly Ser Val Arg Val Val Thr Thr Phe Asp Ala

2945 2950 2955

Glu Tyr Cys Arg His Gly Thr Cys Glu Arg Ser Glu Val Gly Ile 2960 2965 2970

Cys Leu Ser Thr Ser Gly Arg Trp Val Leu Asn Asn Glu His Tyr 2975 2980 2985

Arg Ala Leu Ser Gly Val Phe Cys Gly Val Asp Ala Met Asn Leu 2990 2995 3000

Ile Ala Asn Ile Phe Thr Pro Leu Val Gln Pro Val Gly Ala Leu 3005 3010 3015

Asp Val Ser Ala Ser Val Val Ala Gly Gly Ile Ile Ala Ile Leu 3020 3025 3030

Val Thr Cys Ala Ala Tyr Tyr Phe Met Lys Phe Arg Arg Val Phe 3035 3040 3045

Gly Glu Tyr Asn His Val Val Ala Ala Asn Ala Leu Leu Phe Leu 3050 3055 3060

Met Ser Phe Thr Ile Leu Cys Leu Val Pro Ala Tyr Ser Phe Leu 3065 3070 3075

Pro Gly Val Tyr Ser Val Phe Tyr Leu Tyr Leu Thr Phe Tyr Phe 3080 3085

Thr Asn Asp Val Ser Phe Leu Ala His Leu Gln Trp Phe Ala Met 3095 3100 3105

Phe Ser Pro Ile Val Pro Phe Trp Ile Thr Ala Ile Tyr Val Phe 3110 3115 3120

Cys Ile Ser Leu Lys His Cys His Trp Phe Phe Asn Asn Tyr Leu 3125 3130 3135

Arg Lys Arg Val Met Phe Asn Gly Val Thr Phe Ser Thr Phe Glu 3140 3145 3150

Glu Ala Ala Leu Cys Thr Phe Leu Leu Asn Lys Glu Met Tyr Leu 3155 3160 3165

Lys Leu Arg Ser Glu Thr Leu Leu Pro Leu Thr Gln Tyr Asn Arg 3170 3175 3180

- Tyr Leu Ala Leu Tyr Asn Lys Tyr Lys Tyr Phe Ser Gly Ala Leu 3185 3190 3195
- Asp Thr Thr Ser Tyr Arg Glu Ala Ala Cys Cys His Leu Ala Lys 3200 3205 3210
- Ala Leu Asn Asp Phe Ser Asn Ser Gly Ala Asp Val Leu Tyr Gln 3215 3220 3225
- Pro Pro Gln Thr Ser Ile Thr Ser Ala Val Leu Gln Ser Gly Phe 3230 3235 3240
- Arg Lys Met Ala Phe Pro Ser Gly Lys Val Glu Gly Cys Met Val 3245 3250 3255
- Gln Val Thr Cys Gly Thr Thr Thr Leu Asn Gly Leu Trp Leu Asp 3260 3265 3270
- Asp Thr Val Tyr Cys Pro Arg His Val Ile Cys Thr Ala Glu Asp 3275 3280 3285
- Met Leu Asn Pro Asn Tyr Glu Asp Leu Leu Ile Arg Lys Ser Asn 3290 3295 3300
  - His Ser Phe Leu Val Gln Ala Gly Asn Val Gln Leu Arg Val Ile 3305 3310 3315
  - Gly His Ser Met Gln Asn Cys Leu Leu Arg Leu Lys Val Asp Thr 3320 3335 3330
  - Ser Asn Pro Lys Thr Pro Lys Tyr Lys Phe Val Arg Ile Gln Pro 3335 3340 3345
  - Gly Gln Thr Phe Ser Val Leu Ala Cys Tyr Asn Gly Ser Pro Ser 3350 3360
  - Gly Val Tyr Gln Cys Ala Met Arg Pro Asn His Thr Ile Lys Gly 3365 3370 3375
  - Ser Phe Leu Asn Gly Ser Cys Gly Ser Val Gly Phe Asn Ile Asp 3380 3385 3390
  - Tyr Asp Cys Val Ser Phe Cys Tyr Met His His Met Glu Leu Pro 3395 3400 3405

- Thr Gly Val His Ala Gly Thr Asp Leu Glu Gly Lys Phe Tyr Gly . 3410 3420
- Pro Phe Val Asp Arg Gln Thr Ala Gln Ala Ala Gly Thr Asp Thr 3425 3430 3435
- Thr Ile Thr Leu Asn Val Leu Ala Trp Leu Tyr Ala Ala Val Ile 3440 3445 3450
- Asn Gly Asp Arg Trp Phe Leu Asn Arg Phe Thr Thr Leu Asn 3455 3460 3465
- Asp Phe Asn Leu Val Ala Met Lys Tyr Asn Tyr Glu Pro Leu Thr 3470 3475 3480
- Gln Asp His Val Asp Ile Leu Gly Pro Leu Ser Ala Gln Thr Gly 3485 3490 3495
- Ile Ala Val Leu Asp Met Cys Ala Ala Leu Lys Glu Leu Leu Gln 3500 3505 3510
- Asn Gly Met Asn Gly Arg Thr Ile Leu Gly Ser Thr Ile Leu Glu 3515 3520 3525
- Asp Glu Phe Thr Pro Phe Asp Val Val Arg Gln Cys Ser Gly Val 3530 3540
- Thr Phe Gln Gly Lys Phe Lys Lys Ile Val Lys Gly Thr His His 3545 3550 3555
- Trp Met Leu Leu Thr Phe Leu Thr Ser Leu Leu Ile Leu Val Gln 3560 3565 3570
- Ser Thr Gln Trp Ser Leu Phe Phe Phe Val Tyr Glu Asn Ala Phe 3575 3580 3585
- Leu Pro Phe Thr Leu Gly Ile Met Ala Ile Ala Ala Cys Ala Met 3590 3595 3600
- Leu Leu Val Lys His Lys His Ala Phe Leu Cys Leu Phe Leu Leu 3605 3610 3615
- Pro Ser Leu Ala Thr Val Ala Tyr Phe Asn Met Val Tyr Met Pro 3620 3625 3630

Ser 3635					Thr	Trp	Glu 3645	_	Ala	Asp
		•		•						

- Thr Ser Leu Ser Gly Tyr Arg Leu Lys Asp Cys Val Met Tyr Ala 3650 3655 3660
- Ser Ala Leu Val Leu Leu Ile Leu Met Thr Ala Arg Thr Val Tyr 3665 3670 3675

- Asp Asp Ala Ala Arg Arg Val Trp Thr Leu Met Asn Val Ile Thr 3680 3690
- Leu Val Tyr Lys Val Tyr Tyr Gly Asn Ala Leu Asp Gln Ala Ile 3695 3700 3705
- Ser Met Trp Ala Leu Val Ile Ser Val Thr Ser Asn Tyr Ser Gly 3710 3715 3720
- Val Val Thr Thr Ile Met Phe Leu Ala Arg Ala Ile Val Phe Val 3725 3730 3735
- Cys Val Glu Tyr Tyr Pro Leu Leu Phe Ile Thr Gly Asn Thr Leu 3740 3745 3750
- Gln Cys Ile Met Leu Val Tyr Cys Phe Leu Gly Tyr Cys Cys Cys 3755 3760 3765
- Cys Tyr Phe Gly Leu Phe Cys Leu Leu Asn Arg Tyr Phe Arg Leu 3770 3780
- Thr Leu Gly Val Tyr Asp Tyr Leu Val Ser Thr Gln Glu Phe Arg 3785 3790 3795
- Tyr Met Asn Ser Gln Gly Leu Leu Pro Pro Lys Ser Ser Ile Asp 3800 3805 3810
- Ala Phe Lys Leu Asn Ile Lys Leu Leu Gly Ile Gly Gly Lys Pro 3815 3820 3825
- Cys Ile Lys Val Ala Thr Val Gln Ser Lys Met Ser Asp Val Lys 3830 3840
- Cys Thr Ser Val Val Leu Leu Ser Val Leu Gln Gln Leu Arg Val 3845 3850 3855
- Glu Ser Ser Lys Leu Trp Ala Gln Cys Val Gln Leu His Asn

3865

3870

- Asp Ile Leu Leu Ala Lys Asp Thr Thr Glu Ala Phe Glu Lys Met 3875 3880 3885
- Val Ser Leu Leu Ser Val Leu Leu Ser Met Gln Gly Ala Val Asp 3890 3895 3900
- Ile Asn Arg Leu Cys Glu Glu Met Leu Asp Asn Arg Ala Thr Leu 3905 3910 3915
- Gln Ala Ile Ala Ser Glu Phe Ser Ser Leu Pro Ser Tyr Ala Ala 3920 3925 3930
- Tyr Ala Thr Ala Gln Glu Ala Tyr Glu Gln Ala Val Ala Asn Gly 3935 3940 3945
- Asp Ser Glu Val Val Leu Lys Lys Leu Lys Lys Ser Leu Asn Val 3950 3960
- Ala Lys Ser Glu Phe Asp Arg Asp Ala Ala Met Gln Arg Lys Leu 3965 3970 3975
- Glu Lys Met Ala Asp Gln Ala Met Thr Gln Met Tyr Lys Gln Ala 3980 3985 3990
- Arg Ser Glu Asp Lys Arg Ala Lys Val Thr Ser Ala Met Gln Thr 3995 4000 4005
- Met Leu Phe Thr Met Leu Arg Lys Leu Asp Asn Asp Ala Leu Asn 4010 4015 4020
- Asn Ile Ile Asn Asn Ala Arg Asp Gly Cys Val Pro Leu Asn Ile 4025 4030 4035
- Ile Pro Leu Thr Thr Ala Ala Lys Leu Met Val Val Pro Asp 4040 4045 4050
- Tyr Gly Thr Tyr Lys Asn Thr Cys Asp Gly Asn Thr Phe Thr Tyr 4055 4060 4065
- Ala Ser Ala Leu Trp Glu Ile Gln Gln Val Val Asp Ala Asp Ser 4070 4075 4080
- Lys Ile Val Gln Leu Ser Glu Ile Asn Met Asp Asn Ser Pro Asn 4085 4090 4095

- Leu Ala Trp Pro Leu Ile Val Thr Ala Leu Arg Ala Asn Ser Ala 4100 4105 4110
- Val Lys Leu Gln Asn Asn Glu Leu Ser Pro Val Ala Leu Arg Gln 4115 4120 4125
- Met Ser Cys Ala Ala Gly Thr Thr Gln Thr Ala Cys Thr Asp Asp 4130 4135 4140
- Asn Ala Leu Ala Tyr Tyr Asn Asn Ser Lys Gly Gly Arg Phe Val 4145 4150 4155
- Leu Ala Leu Leu Ser Asp His Gln Asp Leu Lys Trp Ala Arg Phe 4160 4165 4170
- Pro Lys Ser Asp Gly Thr Gly Thr Ile Tyr Thr Glu Leu Glu Pro 4175 4180 4185
- Pro Cys Arg Phe Val Thr Asp Thr Pro Lys Gly Pro Lys Val Lys 4190 4195 4200
- Tyr Leu Tyr Phe Ile Lys Gly Leu Asn Asn Leu Asn Arg Gly Met #205 4210 4215
- Val Leu Gly Ser Leu Ala Ala Thr Val Arg Leu Gln Ala Gly Asn 4220 4225 4230
- Ala Thr Glu Val Pro Ala Asn Ser Thr Val Leu Ser Phe Cys Ala 4235 4240 4245
- Phe Ala Val Asp Pro Ala Lys Ala Tyr Lys Asp Tyr Leu Ala Ser 4250 4255 4260
- Gly Gly Gln Pro Ile Thr Asn Cys Val Lys Met Leu Cys Thr His 4265 4270 4275
- Thr Gly Thr Gly Gln Ala Ile Thr Val Thr Pro Glu Ala Asn Met 4280 4290
- Asp Gln Glu Ser Phe Gly Gly Ala Ser Cys Cys Leu Tyr Cys Arg 4295 4300 4305
- Cys His Ile Asp His Pro Asn Pro Lys Gly Phe Cys Asp Leu Lys 4310 4315 4320

Gly Lys Tyr Val Gln Ile Pro Thr Thr Cys Ala Asn Asp Pro Val 4325 4330 4335

- Gly Phe Thr Leu Arg Asn Thr Val Cys Thr Val Cys Gly Met Trp 4340 4345 4350
- Lys Gly Tyr Gly Cys Ser Cys Asp Gln Leu Arg Glu Pro Leu Met. 4355 4360 4365
- Gln Ser Ala Asp Ala Ser Thr Phe 4370 4375
- <210> 64
- <211> 2697
- <212> PRT
- <213> Severe acute respiratory syndrome virus

<400> 64

- Phe Lys Arg Val Cys Gly Val Ser Ala Ala Arg Leu Thr Pro Cys Gly
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  - Thr Gly Thr Ser Thr Asp Val Val Tyr Arg Ala Phe Asp Ile Tyr Asn 20 25 30
  - Glu Lys Val Ala Gly Phe Ala Lys Phe Leu Lys Thr Asn Cys Cys Arg 35 40 45
  - Phe Gln Glu Lys Asp Glu Glu Gly Asn Leu Leu Asp Ser Tyr Phe Val
  - Val Lys Arg His Thr Met Ser Asn Tyr Gln His Glu Glu Thr Ile Tyr 65 70 75 80
  - Asn Leu Val Lys Asp Cys Pro Ala Val Ala Val His Asp Phe Phe Lys 85 90 95
  - Phe Arg Val Asp Gly Asp Met Val Pro His Ile Ser Arg Gln Arg Leu 100 105 110
  - Thr Lys Tyr Thr Met Ala Asp Leu Val Tyr Ala Leu Arg His Phe Asp 115 120 125
  - Glu Gly Asn Cys Asp Thr Leu Lys Glu Ile Leu Val Thr Tyr Asn Cys 130 140
  - Cys Asp Asp Asp Tyr Phe Asn Lys Lys Asp Trp Tyr Asp Phe Val Glu

145 150 155 160

Asn Pro Asp Ile Leu Arg Val Tyr Ala Asn Leu Gly Glu Arg Val Arg 165 170 175

Gln Ser Leu Leu Lys Thr Val Gln Phe Cys Asp Ala Met Arg Asp Ala 180 185 190

Gly Ile Val Gly Val Leu Thr Leu Asp Asn Gln Asp Leu Asn Gly Asn 195 200 205

Trp Tyr Asp Phe Gly Asp Phe Val Gln Val Ala Pro Gly Cys Gly Val 210 215 220

Pro Ile Val Asp Ser Tyr Tyr Ser Leu Leu Met Pro Ile Leu Thr Leu 225 230 235 240

Thr Arg Ala Leu Ala Ala Glu Ser His Met Asp Ala Asp Leu Ala Lys
245 250 255

Pro Leu Ile Lys Trp Asp Leu Leu Lys Tyr Asp Phe Thr Glu Glu Arg 260 265 270

Leu Cys Leu Phe Asp Arg Tyr Phe Lys Tyr Trp Asp Gln Thr Tyr His 275 280 285

Pro Asn Cys Ile Asn Cys Leu Asp Asp Arg Cys Ile Leu His Cys Ala 290 295 300

Asn Phe Asn Val Leu Phe Ser Thr Val Phe Pro Pro Thr Ser Phe Gly 305 310 315

Pro Leu Val Arg Lys Ile Phe Val Asp Gly Val Pro Phe Val Val Ser 325 330 335

Thr Gly Tyr His Phe Arg Glu Leu Gly Val Val His Asn Gln Asp Val 340 345

Asn Leu His Ser Ser Arg Leu Ser Phe Lys Glu Leu Leu Val Tyr Ala 355 360 365

Ala Asp Pro Ala Met His Ala Ala Ser Gly Asn Leu Leu Leu Asp Lys 370 375 380

Arg Thr Thr Cys Phe Ser Val Ala Ala Leu Thr Asn Asn Val Ala Phe 385 390 395

Gln Thr Val Lys Pro Gly Asn Phe Asn Lys Asp Phe Tyr Asp Phe Ala 405 410 415

Val Ser Lys Gly Phe Phe Lys Glu Gly Ser Ser Val Glu Leu Lys His
420 425 430

Phe Phe Phe Ala Gln Asp Gly Asn Ala Ala Ile Ser Asp Tyr Asp Tyr 445

Tyr Arg Tyr Asn Leu Pro Thr Met Cys Asp Ile Arg Gln Leu Leu Phe 450 455 460

Val Val Glu Val Val Asp Lys Tyr Phe Asp Cys Tyr Asp Gly Gly Cys 465 470 475 480

Ile Asn Ala Asn Gln Val Ile Val Asn Asn Leu Asp Lys Ser Ala Gly
485 490 495

Phe Pro Phe Asn Lys Trp Gly Lys Ala Arg Leu Tyr Tyr Asp Ser Met 500 505 510

Ser Tyr Glu Asp Gln Asp Ala Leu Phe Ala Tyr Thr Lys Arg Asn Val 515 520 525

Ile Pro Thr Ile Thr Gln Met Asn Leu Lys Tyr Ala Ile Ser Ala Lys 530 535 540

Asn Arg Ala Arg Thr Val Ala Gly Val Ser Ile Cys Ser Thr Met Thr 545 550 555 560

Asn Arg Gln Phe His Gln Lys Leu Leu Lys Ser Ile Ala Ala Thr Arg 565 570 575

Gly Ala Thr Val Val Ile Gly Thr Ser Lys Phe Tyr Gly Gly Trp His 580 585 590

Asn Met Leu Lys Thr Val Tyr Ser Asp Val Glu Thr Pro His Leu Met 595 600 605

Gly Trp Asp Tyr Pro Lys Cys Asp Arg Ala Met Pro Asn Met Leu Arg 610 620

Ile Met Ala Ser Leu Val Leu Ala Arg Lys His Asn Thr Cys Cys Asn 625 630 635 640

Leu	Ser	His	Arg	Phe	Tyr	Arg	Leu	Ala	Asn	Glu	Cys	Ala	Gln	Val	Leu
				645	•				650		٠.	•		655	

- Ser Glu Met Val Met Cys Gly Gly Ser Leu Tyr Val Lys Pro Gly Gly 660 . 665 670
- Thr Ser Ser Gly Asp Ala Thr Thr Ala Tyr Ala Asn Ser Val Phe Asn 675 680 685
- Ile Cys Gln Ala Val Thr Ala Asn Val Asn Ala Leu Leu Ser Thr Asp 690 695 700
- Gly Asn Lys Ile Ala Asp Lys Tyr Val Arg Asn Leu Gln His Arg Leu 705 710 715 720
- Tyr Glu Cys Leu Tyr Arg Asn Arg Asp Val Asp His Glu Phe Val Asp 725 730 735
- Glu Phe Tyr Ala Tyr Leu Arg Lys His Phe Ser Met Met Ile Leu Ser 740 745 750
- Asp Asp Ala Val Val Cys Tyr Asn Ser Asn Tyr Ala Ala Gln Gly Leu 755 760 765
- Val Ala Ser Ile Lys Asn Phe Lys Ala Val Leu Tyr Tyr Gln Asn Asn 775 780
- Val Phe Met Ser Glu Ala Lys Cys Trp Thr Glu Thr Asp Leu Thr Lys 785 790 795 800
- Gly Pro His Glu Phe Cys Ser Gln His Thr Met Leu Val Lys Gln Gly 805 810 815
- Asp Asp Tyr Val Tyr Leu Pro Tyr Pro Asp Pro Ser Arg Ile Leu Gly 820 825 830
- Ala Gly Cys Phe Val Asp Asp Ile Val Lys Thr Asp Gly Thr Leu Met 835 840 845
- Ile Glu Arg Phe Val Ser Leu Ala Ile Asp Ala Tyr Pro Leu Thr Lys 850 855 860
- His Pro Asn Gln Glu Tyr Ala Asp Val Phe His Leu Tyr Leu Gln Tyr 865 870 875 880

Ile Arg Lys Leu His Asp Glu Leu Thr Gly His Met Leu Asp Met Tyr 885 890 895

- Ser Val Met Leu Thr Asn Asp Asn Thr Ser Arg Tyr Trp Glu Pro Glu 900 905 910
- Phe Tyr Glu Ala Met Tyr Thr Pro His Thr Val Leu Gln Ala Val Gly 915 925
- Ala Cys Val Leu Cys Asn Ser Gln Thr Ser Leu Arg Cys Gly Ala Cys 930 935 940
- Ile Arg Arg Pro Phe Leu Cys Cys Lys Cys Cys Tyr Asp His Val Ile 945 950 955 960
- Ser Thr Ser His Lys Leu Val Leu Ser Val Asn Pro Tyr Val Cys Asn 965 970 975
- Ala Pro Gly Cys Asp Val Thr Asp Val Thr Gln Leu Tyr Leu Gly Gly 980 985 990
- Met Ser Tyr Tyr Cys Lys Ser His Lys Pro Pro Ile Ser Phe Pro Leu ' 995 1000 1005
- Cys Ala Asn Gly Gln Val Phe Gly Leu Tyr Lys Asn Thr Cys Val 1010 1015 1020
- Gly Ser Asp Asn Val Thr Asp Phe Asn Ala Ile Ala Thr Cys Asp 1025 1030 1035
- Trp Thr Asn Ala Gly Asp Tyr Ile Leu Ala Asn Thr Cys Thr Glu 1040 1045 1050
- Arg Leu Lys Leu Phe Ala Ala Glu Thr Leu Lys Ala Thr Glu Glu 1055 1060 1065
- Thr Phe Lys Leu Ser Tyr Gly Ile Ala Thr Val Arg Glu Val Leu 1070 1080
- Ser Asp Arg Glu Leu His Leu Ser Trp Glu Val Gly Lys Pro Arg 1085 1090 1095
- Pro Pro Leu Asn Arg Asn Tyr Val Phe Thr Gly Tyr Arg Val Thr 1100 1105 1110
- Lys Asn Ser Lys Val Gln Ile Gly Glu Tyr Thr Phe Glu Lys Gly

1115 1120 1125

Asp Tyr Gly Asp Ala Val Val Tyr Arg Gly Thr Thr Tyr Lys 1130 1135 1140

- Leu Asn Val Gly Asp Tyr Phe Val Leu Thr Ser His Thr Val Met 1145 1150 1155
- Pro Leu Ser Ala Pro Thr Leu Val Pro Gln Glu His Tyr Val Arg 1160 1165 1170
- Ile Thr Gly Leu Tyr Pro Thr Leu Asn Ile Ser Asp Glu Phe Ser 1175 1180 1185
- Ser Asn Val Ala Asn Tyr Gln Lys Val Gly Met Gln Lys Tyr Ser 1190 1195 1200
- Thr Leu Gln Gly Pro Pro Gly Thr Gly Lys Ser His Phe Ala Ile 1205 1210 1215
- Gly Leu Ala Leu Tyr Tyr Pro Ser Ala Arg Ile Val Tyr Thr Ala 1220 1225 1230
- Cys Ser His Ala Ala Val Asp Ala Leu Cys Glu Lys Ala Leu Lys 1235 1240 1245

1

- Tyr Leu Pro Ile Asp Lys Cys Ser Arg Ile Ile Pro Ala Arg Ala 1250 1255 1260
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- Gln Tyr Val Phe Cys Thr Val Asn Ala Leu Pro Glu Thr Thr Ala 1280 1285 1290
- Asp Ile Val Val Phe Asp Glu Ile Ser Met Ala Thr Asn Tyr Asp 1295 1300 1305
- Leu Ser. Val Val Asn Ala Arg Leu Arg Ala Lys His Tyr Val Tyr 1310 1315 1320
- Ile Gly Asp Pro Ala Gln Leu Pro Ala Pro Arg Thr Leu Leu Thr 1325 1330 1335
- Lys Gly Thr Leu Glu Pro Glu Tyr Phe Asn Ser Val Cys Arg Leu 1340 1345 1350

Met Lys Thr Ile Gly Pro Asp Met Phe Leu Gly Thr Cys Arg Arg 1355 1360 Cys Pro Ala Glu Ile Val Asp Thr Val Ser Ala Leu Val Tyr Asp 1370 1375 1380 ' Asn Lys Leu Lys Ala His Lys Asp Lys Ser Ala Gln Cys Phe Lys 1385 1390 Met Phe Tyr Lys Gly Val Ile Thr His Asp Val Ser Ser Ala Ile 1400 1405 1410 Asn Arg Pro Gln 11e Gly Val Val Arg Glu Phe Leu Thr Arg Asn 1415 1420 Pro Ala Trp Arg Lys Ala Val Phe Ile Ser Pro Tyr Asn Ser Gln 1430 1435 1440 Asn Ala Val Ala Ser Lys Ile Leu Gly Leu Pro Thr Gln Thr Val 1445 1450 1455 Asp Ser Ser Gln Gly Ser Glu Tyr Asp Tyr Val Ile Phe Thr Gln 1460 1465 1470 Thr Thr Glu Thr Ala His Ser Cys Asn Val Asn Arg Phe Asn Val 1475 1480 Ala Ile Thr Arg Ala Lys Ile Gly Ile Leu Cys Ile Met Ser Asp 1490 1495 ' 1500 Arg Asp Leu Tyr Asp Lys Leu Gln Phe Thr Ser Leu Glu Ile Pro 1505 1515 Arg Arg Asn Val Ala Thr Leu Gln Ala Glu Asn Val Thr Gly Leu 1520 1,525 1530 Phe Lys Asp Cys Ser Lys Ile Ile Thr Gly Leu His Pro Thr Gln 1535 1545 Ala Pro Thr His Leu Ser Val Asp Ile Lys Phe Lys Thr Glu Gly 1550 1555 Leu Cys Val Asp Ile Pro Gly Ile Pro Lys Asp Met Thr Tyr Arg 1565

Arg Leu Ile Ser Met Met Gly Phe Lys Met Asn Tyr Gln Val Asn 1580 1585 1590

- Gly Tyr Pro Asn Met Phe Ile Thr Arg Glu Glu Ala Ile Arg His 1595 1600 1605
- Val Arg Ala Trp Ile Gly Phe Asp Val Glu Gly Cys His Ala Thr 1610 1615 1620
- Arg Asp Ala Val Gly Thr Asn Leu Pro Leu Gln Leu Gly Phe Ser 1625 1630 1635
- Thr Gly Val Asn Leu Val Ala Val Pro Thr Gly Tyr Val Asp Thr 1640 1650
- Glu Asn Asn Thr Glu Phe Thr Arg Val Asn Ala Lys. Pro Pro Pro 1655 1660 1665
- Gly Asp Gln Phe Lys His Leu Ile Pro Leu Met Tyr Lys Gly Leu 1670 1680
- Pro Trp Asn Val Val Arg Ile Lys Ile Val Gln Met Leu Ser Asp 1685 1690 1695
- Thr Leu Lys Gly Leu Ser Asp Arg Val Val Phe Val Leu Trp Ala 1700 1705 1710
- His Gly. Phe Glu Leu Thr Ser Met Lys Tyr Phe Val Lys Ile Gly
  1715 1720 1725
- Pro Glu Arg Thr Cys Cys Leu Cys Asp Lys Arg Ala Thr Cys Phe 1730 1735 1740
- Ser Thr Ser Ser Asp Thr Tyr Ala Cys Trp Asn His Ser Val Gly 1745 1750 1755
- Phe Asp Tyr Val Tyr Asn Pro Phe Met Ile Asp Val Gln Gln Trp 1760 1770
- Gly Phe Thr Gly Asn Leu Gln Ser Asn His Asp Gln His Cys Gln 1775 1780 1785
- Val His Gly Asn Ala His Val Ala Ser Cys Asp Ala Ile Met Thr 1790 1795 1800

Arg Cys Leu Ala Val His Glu Cys Phe Val Lys Arg Val Asp Trp 1805 1810 1815

- Ser Val Glu Tyr Pro Ile Ile Gly Asp Glu Leu Arg Val Asn Ser 1820 1825 1830
- Ala Cys Arg Lys Val Gln His Met Val Val Lys Ser Ala Leu Leu 1835 1840 1845
- Ala Asp Lys Phe Pro Val Leu His Asp Ile Gly Asn Pro Lys Ala 1850 1855 1860
- Ile Lys Cys Val Pro Gln Ala Glu Val Glu Trp Lys Phe Tyr Asp 1865 1870 1875
- Ala Gln Pro Cys Ser Asp Lys Ala Tyr Lys Ile Glu Glu Leu Phe 1880 1885 1890
- Tyr Ser Tyr Ala Thr His His Asp Lys Phe Thr Asp Gly Val Cys 1895 1900 1905
- Leu Phe Trp Asn Cys Asn Val Asp Arg Tyr Pro Ala Asn Ala Ile 1910 1915 1920
- Val Cys Arg Phe Asp Thr Arg Val Leu Ser Asn Leu Asn Leu Pro 1925 1930 1935
- Gly Cys Asp Gly Gly Ser Leu Tyr Val Asn Lys His Ala Phe His 1940 1945 1950
- Thr Pro Ala Phe Asp Lys Ser Ala Phe Thr Asn Leu Lys Gln Leu 1955 1960 1965
- Pro Phe Phe Tyr Tyr Ser Asp Ser Pro Cys Glu Ser His Gly Lys 1970 1975 1980
- Gln Val Val Ser Asp Ile Asp Tyr Val Pro Leu Lys Ser Ala Thr 1985 1990 1995
- Cys Ile Thr Arg Cys Asn Leu Gly Gly Ala Val Cys Arg His His 2000 2005 2010
- Ala Asn Glu Tyr Arg Gln Tyr Leu Asp Ala Tyr Asn Met Met Ile 2015 2020 2025
- Ser Ala Gly Phe Ser Leu Trp Ile Tyr Lys Gln Phe Asp Thr Tyr

2030

2035

2040

- Asn Leu Trp Asn Thr Phe Thr Arg Leu Gln Ser Leu Glu Asn Val . 2045 2050 2055
- Ala Tyr Asn Val Val Asn Lys Gly His Phe Asp Gly His Ala Gly 2060 2065 2070
- Glu Ala Pro Val Ser Ile Ile Asn Asn Ala Val Tyr Thr Lys Val 2075 2080 2085
- Asp Gly Ile Asp Val Glu Ile Phe Glu Asn Lys Thr Thr Leu Pro 2090 2095 2100
- Val Asn Val Ala Phe Glu Leu Trp Ala Lys Arg Asn Ile Lys Pro 2105 2110 2115
- Val Pro Glu Ile Lys Ile Leu Asn Asn Leu Gly Val Asp Ile Ala 2120 2125 2130
  - Ala Asn Thr Val Ile Trp Asp Tyr Lys Arg Glu Ala Pro Ala His 2135 2140 2145
  - Val Ser Thr Ile Gly Val Cys Thr Met Thr Asp Ile Ala Lys Lys 2150 2160
  - Pro Thr Glu Ser Ala Cys Ser Ser Leu Thr Val Leu Phe Asp Gly 2165 2170 2175
  - Arg Val Glu Gly Gln Val Asp Leu Phe Arg Asn Ala Arg Asn Gly 2180 2185 2190
  - Val Leu Ile Thr Glu Gly Ser Val Lys Gly Leu Thr Pro Ser Lys 2195 2200 2205
  - Gly Pro Ala Gln Ala Ser Val Asn Gly Val Thr Leu Ile Gly Glu 2210 2215 2220
  - Ser Val Lys Thr Gln Phe Asn Tyr Phe Lys Lys Val Asp Gly Ile 2225 2230 2235
  - Ile Gln Gln Leu Pro Glu Thr Tyr Phe Thr Gln Ser Arg Asp Leu 2240 2245 2250
  - Glu Asp Phe Lys Pro Arg Ser Gln Met Glu Thr Asp Phe Leu Glu 2255 2260 2265

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Leu	Ala 2270	Met	Asp	Glu	Phe.	Ile 2275	Gln	Arg	Tyr		Leu 2280	Glu	Gly	Tyr
Ala	Phe 2285	Glu	His	,Ile	Val	Tyr 2290	Gly	Asp	Phe	Ser	His 2295	Gly	Gln	Leu
СjУ	Gly 2300	Leu	His	Leu	Met	Ile 2305	Gly	Leu	Ala	Lys	Arg 2310	Ser	Gln	Asp
Ser	Pro 2315	Leu	Lys	Leu	Glu ·	Asp 2320	Phe	Ile	Pro	Met	Asp 2325		Thr	Val
Lys	Asn 2330	Tyr	Phe	Ile	Thr	Asp 2335	Ala	Gln	Thr	GĨy	Ser 2340	Ser	Lys	Cys
Val	Cys 2345	Ser	Val ∙.	Ile	Asp	Leu 2350	Leu	Leu	Asp	Asp	Phe 2355	Val	Glu	Ile
Ile	Lys 2360	Ser	Gĺn	Ąsp	Leu	Ser 2365	Val	Ile	Ser		Val 2370	Val	Lys	Val
Thr	Ile 2375	Asp	Tyr	·Ala	Glu <sub>.</sub>	Ile 2380	Ser	Phe	Met		Trp 2385	Cys	Lys	Asp
Gly	His 2390	Val	Glu	Thr	Phe	Tyr 2395	Pro	Lys	Leu	Gln	Ala 2400	Ser	Gln	Ala
Trp	Gln 2405	Pro	Gly	Val	Ala	Met 2410	Pro	Asn	Leu	Tyr	Lys 2415	Met	Gln	Arg
Met	Leu 2420	Leu	Glu	Lys		Asp 2425	Leu	Gln	Asn	Tyr	Gly 2430	Glu	Asn	Ala
Val	Ile 2435	Pro	Lys	Gly	Ile	Met 2440	Met	Asn	Val	Ala	Lys 2445	Tyr	Thr	Gln
Leu	Cys 2450	Gln	Tyr	Leu	Asn	Thr 2455	Leu	Thr	Leu	Ala	Val 2460	Pro	Tyr	Asn
Met	Arg 2465	Val	Ile	His	Phe	Gly 2470	Ala	Gly	Ser	Asp	Lys 2475	Gly	Val	Ala
Pro	Gly 2480	Thr	Ala	Val	Leu	Arg 2485	Gln	Trp	Leu	Pro	Thr 2490	Gly	Thr	Leu

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Leu Val Asp Ser Asp Leu Asn Asp Phe Val Ser Asp Ala Asp Ser 2495 2500 2505

- Thr Leu Ile Gly Asp Cys Ala Thr Val His Thr Ala Asn Lys Trp 2510 2520
- Asp Leu Ile Ile Ser Asp Met Tyr Asp Pro Arg Thr Lys His Val 2525 2530 2535
- Thr Lys Glu Asn Asp Ser Lys Glu Gly Phe Phe Thr Tyr Leu Cys 2540 2545 2550
- Gly Phe Ile Lys Gln Lys Leu Ala Leu Gly Gly Ser Ile Ala Val 2555 2560 2565
- Lys Ile Thr Glu His Ser Trp Asn Ala Asp Leu Tyr Lys Leu Met 2570 2580
- Gly His Phe Ser Trp Trp Thr Ala Phe Val Thr Asn Val Asn Ala 2585 2590 2595
- Ser Ser Ser Glu Ala Phe Leu Ile Gly Ala Asn Tyr Leu Gly Lys 2600 2605 2610
- Pro Lys Glu Gln Ile Asp Gly Tyr Thr Met His Ala Asn Tyr Ile 2615 2620 2625
- Phe Trp Arg Asn Thr Asn Pro Ile Gln Leu Ser Ser Tyr Ser Leu 2630 2635 2640
- Phe Asp Met Ser Lys Phe Pro Leu Lys Leu Arg Gly Thr Ala Val 2645 2650 2655
- Met Ser Leu Lys Glu Asn Gln Ile Asn Asp Met Ile Tyr Ser Leu 2660 2665 2670
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- <210> 65
- <211> 274
- <212> PRT
- <213> Severe acute respiratory syndrome virus

<400> 65

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Gly Val Ala Phe Leu Ala Val Phe Gln Ser Ala Thr Lys Ile Ile Ala 50 55 60

Leu Asn Lys Arg Trp Gln Leu Ala Leu Tyr Lys Gly Phe Gln Phe IIe 65 70 75 80

Cys Asn Leu Leu Leu Phe Val Thr Ile Tyr Ser His Leu Leu 85 90 95

Val Ala Ala Gly Met Glu Ala Gln Phe Leu Tyr Leu Tyr Ala Leu Ile 100 105 110

Tyr Phe Leu Gln Cys Ile Asn Ala Cys Arg Ile Ile Met Arg Cys Trp
115 120 125

Leu Cys Trp Lys Cys Lys Ser Lys Asn Pro Leu Leu Tyr Asp Ala Asn 130 135 140

Tyr Phe Val Cys Trp His Thr His Asn Tyr Asp Tyr Cys Ile Pro Tyr 155 160

Asn Ser Val Thr Asp Thr Ile Val Val Thr Glu Gly Asp Gly Ile Ser 165 170 175

Thr Pro Lys Leu Lys Glu Asp Tyr Gln Ile Gly Gly Tyr Ser Glu Asp 180 185 190

Arg His Ser Gly Val Lys Asp Tyr Val Val Val His Gly Tyr Phe Thr 195 200 205

Glu Val Tyr Tyr Gln Leu Glu Ser Thr Gln Ile Thr Thr Asp Thr Gly 210 215 220

Ile Glu Asn Ala Thr Phe Phe Ile Phe Asn Lys Leu Val Lys Asp Pro 225 230 235 240

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Pro Leu

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<213> Severe acute respiratory syndrome virus

<400> 66

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Ile Leu Arg' Ile Gly Thr Gln Val Leu Lys Thr Met Ser Leu Tyr Met 50 55 60 · .

Ala Ile Ser Pro Lys Phe Thr Thr Ser Leu Ser Leu His Lys Leu Leu 70 75

Gln Thr Leu Val Leu Lys Met Leu His Ser Ser Ser Leu Thr Ser Leu 90

Leu Lys Thr His Arg Met Cys Lys Tyr Thr Gln Ser Thr Ala Leu Gln 100 105 110

Glu Leu Leu Ile Gln Gln Trp Ile Gln Phe Met Met Ser Arg Arg 115 120 125

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Thr His Ser Phe Arg Lys Lys Gln Val Arg 145 150

<210> 67

<211> 63

<212> PRT

<213> Severe acute respiratory syndrome virus

<400> 67

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<210> 68

<211> 122

<212> PRT .

<213> Severe acute respiratory syndrome virus

<400> 68

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Leu Ala Asp Asn Lys Phe Ala Leu Thr Cys Thr Ser Thr His Phe Ala

Phe Ala Cys Ala Asp Gly Thr Arg His Thr Tyr Gln Leu Arg Ala Arg . 75

Ser Val Ser Pro Lys Leu Phe Ile Arg Gln Glu Glu Val Gln Glu 85 90

Leu Tyr Ser Pro Leu Phe Leu Ile Val Ala Ala Leu Val Phe Leu Ile 100 .

Leu Cys Phe Thr Ile Lys Arg Lys Thr Glu 115

<210> 69

<211> 44

<212> PRT

<213> Severe acute respiratory syndrome virus

<400> 69

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<211> 39

<212> PRT

<213> Severe acute respiratory syndrome virus

<4.00> 70

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Asp Pro Cys Lys Val Gln His 35

<210> 71

<211> 84

<212> PRT

<213> Severe acute respiratory syndrome virus

<400> 71

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20 25 30

Trp His Thr Met Val Gln Thr Cys Thr Pro Asn Val Thr Ile Asn Cys
35 40

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Glu Gly His Gln Thr Ala Ala Phe Arg Asp Val Leu Val Val Leu Asn 75

Lys Arg Thr Asn

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<213> Severe acute respiratory syndrome virus

<400> .72

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Leu Gly Ser Gln Leu Ser Leu Ser Met Ala Arg Arg Asn Leu Asp Ser 50 55 60

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Ala Lys

<210> 73 <211> 70

<212> PRT <213> Severe acute respiratory syndrome virus

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Pro His His Val Val Ala Val Ile Gln Glu Ile Gln Leu Leu Ala Ala 40

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His Leu Leu Val Ala Ala 20

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<212> PRT

<213> Severe acute respiratory syndrome virus

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Asn Ala Cys Arg Ile Ile Met

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<213> Severe acute respiratory syndrome virus

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Ile Leu

<210> 80

<211> 23

<212> PRT

<213> Severe acute respiratory syndrome virus

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<210> 81

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<213> Severe acute respiratory syndrome virus

<400> 81

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<210> 82

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<213> Severe acute respiratory syndrome virus

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<210> 83

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<210> 84

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Phe Thr Ile

<210> 86

<211> 83

<212> PRT

<213> Severe acute respiratory syndrome virus

<400> 86

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Pro Leu Ala Asp Asn Lys Phe Ala Leu Thr Cys Thr Ser Thr His Phe 35 40 45

Ala Phe Ala Cys Ala Asp Gly Thr Arg His Thr Tyr Gln Leu Arg Ala 50 55 60

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Glu Leu Tyr

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<213> Artificial Sequence

<220>

<223> Primer ·

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37

37

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WO 2004/096842		•	•	PCT/CA2004	/0006 <b>26</b>
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Thr Asp Thr Gly Ile Glu Asn Ala Thr Phe Phe Ile Phe Asn Lys Leu 100 105 110

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- Ala Gln Asp Ile Trp Gly Thr Ser Ala Ala Ala Tyr Phe Val Gly Tyr 245 250 255
- Leu Lys Pro Thr Thr Phe Met Leu Lys Tyr Asp Glu Asn Gly Thr Ile 260 265 270
- Thr Asp Ala Val Asp Cys Ser Gln Asn Pro Leu Ala Glu Leu Lys Cys 275 280 285
- Ser Val Lys Ser Phe Glu Ile Asp Lys Gly Ile Tyr Gln Thr Ser Asn 290 295 300 .
- Phe Arg Val Val Pro Ser Gly Asp Val Val Arg Phe Pro Asn Ile Thr 305 310' 315
- Asn Leu Cys Pro Phe Gly Glu Val Phe Asn Ala Thr Lys Phe Pro Ser

325

330

335

Val Tyr Ala Trp Glu Arg Lys Lys Ile Ser Asn Cys Val Ala Asp Tyr 340 345 350

Ser Val Leu Tyr'Asn Ser Thr Phe Phe Ser Thr Phe Lys Cys Tyr Gly 355 360 365

Val Ser Ala Thr Lys Leu Asn Asp Leu Cys Phe Ser Asn Val Tyr Ala 370 375 380

Asp Ser Phe Val Val Lys Gly Asp Asp Val Arg Gln Ile Ala Pro Gly 385 390 395 400

Gln Thr Gly Val Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe
405 410 415

Met Gly Cys Val Leu Ala Trp Asn Thr Arg Asn Ile Asp Ala Thr Ser 420 425 430

Thr Gly Asn Tyr Asn Tyr Lys Tyr Arg Tyr Leu Arg His Gly Lys Leu
435 440 445

Arg Pro Phe Glu Arg Asp Ile Ser Asn Val Pro Phe Ser Pro Asp Gly 450 455 460

Lys Pro Cys Thr Pro Pro Ala Leu Asn Cys Tyr Trp Pro Leu Asn Asp 465 470 475 480

Tyr Gly Phe Tyr Thr Thr Gly Ile Gly Tyr Gln Pro Tyr Arg Val 485 490 495

Val Val Leu Ser Phe Glu Leu Leu Asn Ala Pro Ala Thr Val Cys Gly 500 505 510

Pro Lys Leu Ser Thr Asp Leu Ile Lys Asn Gln Cys Val Asn Phe Asn 515 520 525

Phe Asn Gly Leu Thr Gly Thr Gly Val Leu Thr Pro Ser Ser Lys Arg 530 535

Phe Gln Pro Phe Gln Gln Phe Gly Arg Asp Val Ser Asp Phe Thr Asp 545 550 555 560

Ser Val Arg Asp Pro Lys Thr Ser Glu Ile Leu Asp Ile Ser Pro Cys 565 570 575

Ala	Phe	Gly	Gly	Val	Ser	Val	Iļe	Thr	Pro	Gly	Thr	·Asn	Ala	Ser	Ser
			580		·			585					590	•	

- Glu Val Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Asp Val Ser Thr 595 600 605
- Ala Ile His Ala Asp Gln Leu Thr Pro Ala Trp Arg Ile Tyr Ser Thr 610 615 620
- Gly Asn Asn Val Phe Gln Thr Gln Ala Gly Cys Leu Ile Gly Ala Glu 625 . 630 635 640
- His Val Asp Thr Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile
  645 650 655
- Cys Ala Ser Tyr His Thr Val Ser Leu Leu Arg Ser Thr Ser Gln Lys
  660 665 670
- Ser Ile Val Ala Tyr Thr Met Ser Leu Gly Ala Asp Ser Ser Ile Ala 675 680 685
- Tyr Ser Asn Asn Thr Ile Ala Ile Pro Thr Asn Phe Ser Ile Ser Ile 690 695 700
- Thr Thr Glu Val Met Pro Val Ser Met Ala Lys Thr Ser Val Asp Cys 705 710 715 720
- Asn Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ala Asn Leu Leu 725 730 735
- Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Ser Gly Ile 740 745 750
- Ala Ala Glu Gln Asp Arg Asn Thr Arg Glu Val Phe Ala Gln Val Lys
  755 760 765
- Gln Met Tyr Lys Thr Pro Thr Leu Lys Tyr Phe Gly Gly Phe Asn Phe 770 780
- Ser Gln Ile Leu Pro Asp Pro Leu Lys Pro Thr Lys Arg Ser Phe Ile 785 790 795 800
- Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Met 805 810 815

Lys Gln Tyr Gly Glu Cys Leu Gly Asp Ile Asn Ala Arg Asp Leu Ile 820 825 830

- Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr 835 , 840 845
- Asp Asp Met Ile Ala Ala Tyr Thr Ala Ala Leu Val Ser Gly Thr Ala 850 860
- Thr Ala Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe 865 870 875 880
- Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn 885 890 895
- Val Leu Tyr Glu Asn Gln Lys Gln Ile Ala Asn Gln Phe Asn Lys Ala 900 905 910
- Ile Ser Gln Ile Gln Glu Ser Leu Thr Thr Thr Ser Thr Ala Leu Gly 915 920 925
- Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu 930 935 940
- Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn 945 950 955 960
- Asp Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln Ile Asp 965 970 975
- Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln 980 985 990
- Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala 995 1000 1005
- Thr Lys Met Ser Glu Cys Val Leu Gly Gln Ser Lys Arg Val Asp 1010 1015 1020
- Phe Cys Gly Lys Gly Tyr His Leu Met Ser Phe Pro Gln Ala Ala 1025 1030 1035
- Pro His Gly Val Val Phe Leu His Val Thr Tyr Val Pro Ser Gln 1040 1045 1050

Glu Arg Asn Phe Thr Thr Ala Pro Ala Ile Cys His Glu Gly Lys 1055 1060 1065

- Ala Tyr Phe Pro Arg Glu Gly Val Phe Val Phe Asn Gly Thr Ser 1070 1075 1080
- Trp Phe Ile Thr Gln Arg Asn Phe Phe Ser Pro Gln Ile Ile Thr 1085 1090 1095
- Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly 1100 1105 1110
- Ile Ile Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp 1115 1120 1125
- Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser 1130 1135 1140
- Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val 1145 1150 1155
- Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys 1160 1165 1170
- Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr 1175 1180 1185
- Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Val Trp Leu Gly Phe Ile 1190 1195 1200
- Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Leu Leu Cys Cys 1205 1210 1215
- Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Ala Cys Ser Cys Gly 1220 1225 1230
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- Gly Val Lys Leu His Tyr Thr 1250 1255
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- <211> 422
- <212> PRT
- <213> Severe acute respiratory syndrome virus

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<400> 204

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Thr Phe Gly Gly Pro Thr Asp Ser Thr Asp Asn Asn Gln Asn Gly Gly 20''' 25 30

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Asn Thr Ala Ser Trp Phe Thr Ala Leu Thr Gln His Gly Lys Glu Glu 50 55 60

Leu Arg Phe Pro Arg Gly Gln Gly Val Pro Ile Asn Thr Asn Ser Gly 65 70 75 80

Pro Asp Asp Gln' Ile Gly Tyr Tyr Arg Arg Ala Thr Arg Arg Val Arg 85 90 95

Gly Gly Asp Gly Lys Met Lys Glu Leu Ser Pro Arg Trp Tyr Phe Tyr 100 105 110

Tyr Leu Gly Thr Gly Pro Glu Ala Ser Leu Pro Tyr Gly Ala Asn Lys 115 120 125

Glu Gly Tle Val Trp Val Ala Thr Glu Gly Ala Leu Asn Thr Pro Lys 130 135 140

Asp His Ile Gly Thr Arg Asn Pro Asn Asn Asn Ala Ala Thr Val Leu 145 150 155 160

Gln Leu Pro Gln Gly Thr Thr Leu Pro Lys Gly Phe Tyr Ala Glu Gly 165 170 175

Ser Arg Gly Gly Ser Gln Ala Ser Ser Arg Ser Ser Ser Arg Ser Arg 180 185 190

Gly Asn Ser Arg Asn Ser Thr Pro Gly Ser Ser Arg Gly Asn Ser Pro 195 200 205

Ala Arg Met Ala Ser Gly Gly Gly Glu Thr Ala Leu Ala Leu Leu Leu 210 215 220

Leu Asp Arg Leu Asn Gln Leu Glu Ser Lys Val Ser Gly Lys Gly Gln 225 230 235 240

Gln Gln Gln Gly Gln Thr Val Thr Lys Lys Ser Ala Ala Glu Ala Ser 245 250

Lys Lys Pro Arg Gln Lys Arg Thr Ala Thr Lys Gln Tyr Asn Val Thr 260 , 265

Gln Ala Phe Gly Arg Arg Gly Pro Glu Gln Thr Gln Gly Asn Phe Gly 280 . 285

Asp Gln Asp Leu Ile Arg Gln Gly Thr Asp Tyr Lys His Trp Pro Gln · 290

Ile Ala Gln Phe Ala Pro Ser Ala Ser Ala Phe Phe Gly Met Ser Arg 310

Ile Gly Met Glu Val Thr Pro Ser Gly Thr Trp Leu Thr Tyr His Gly

Ala Ile Lys Leu Asp Asp Lys Asp Pro Gln Phe Lys Asp Asn Val Ile 345

Leu Leu Asn Lys His Ile Asp Ala Tyr Lys Thr Phe Pro Pro Thr Glu 355 360 365

Pro Lys Lys Asp Lys Lys Lys Thr Asp Glu Ala Gln Pro Leu Pro 375

Gln Arg Gln Lys Lys Gln Pro Thr Val Thr Leu Leu Pro Ala Ala Asp 390 395

Met Asp Asp Phe Ser Arg Gln Leu Gln Asn Ser Met Ser Gly Ala Ser 405

Ala Asp Ser Thr Gln Ala

<210> 205 <211> 221 <212> PRT <213> Sars associated coronavirus

<400> 205

Met Ala Asp Asn Gly Thr Ile Thr Val Glu Glu Leu Lys Gln Leu Leu-

Glu Gln Trp Asn Leu Val Ile Gly Phe Leu Phe Leu Ala Trp Ile Met

30

Leu Leu Gln Phe Ala Tyr Ser Asn Arg Asn Arg Phe Leu Tyr Ile Ile 40

Lys Leu Val Phe Leu Trp Leu Leu Trp Pro Val Thr Leu Ala Cys Phe. 55

Val Leu Ala Ala Val Tyr Arg Ile Asn Trp Val Thr Gly Gly Ile Ala 75 70

Ile Ala Met Ala Cys Ile Val Gly Leu Met Trp Leu Ser Tyr Phe Val 90

Ala Ser Phe Arg Leu Phe Ala Arg Thr Arg Ser Met Trp Ser Phe Asn 100 105 110

Pro Glu Thr Asn Ile Leu Leu Asn Val Pro Leu Arg Gly Thr Ile Val 120 · 125

Thr Arg Pro Leu Met Glu Ser Glu Leu Val Ile Gly Ala Val Ile Ile 130 135 140

Arg Gly His Leu Arg Met Ala Gly His Ser Leu Gly Arg Cys Asp Ile 155 ·

Lys Asp Leu Pro Lys Glu Ile Thr Val Ala Thr Ser Arg Thr Leu Ser 165 170

Tyr Tyr Lys Leu Gly Ala Ser Gln Arg Val Gly Thr Asp Ser Gly Phe 180 185

Ala Ala Tyr Asn Arg Tyr Arg Ile Gly Asn Tyr Lys Leu Asn Thr Asp . 200

His Ala Gly Ser Asn Asp Asn Ile Ala Leu Leu Val Gln 210 215

<210> 206

<211> 76 <212> PRT

<213> Severe acute respiratory syndrome virus

<400> 206

Met Tyr Ser Phe Val Ser Glu Glu Thr Gly Thr Leu Ile Val Asn Ser

Val Leu Leu Phe Leu Ala Phe Val Val Phe Leu Leu Val Thr Leu Ala 20 25 30

Ile Leu Thr Ala Leu Arg Leu Cys Ala Tyr Cys Cys Asn Ile Val Asn 35 40 45

Val Ser Leu Val Lys Pro Thr Val Tyr Val Tyr Ser Arg Val Lys Asn 50 60

Leu Asn Ser Ser Glu Gly Val Pro Asp Leu Leu Val 65 70 .75

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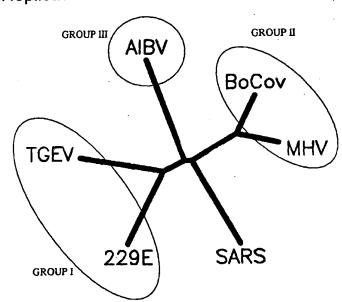
R3P 2G6 (CA). LI, Yan [CA/CA]; 59 Forestgate Avenue, Winnipeg, Manitoba R3P 2L3 (CA). BASTIEN, Nathalie [CA/CA]; 2501-170 Hargrave Street, Winnipeg, Manitoba R3C-3H4 (CA). BRUNHAM, Robert [CA/CA]; 1919 Whyte Avenue, Vancouver, British Columbia V6J 1B4 (CA). BROOKS-WILSON, Angela [CA/CA]; 7100 Langton Road, Richmond, British Columbia V7C 4B2 (CA). HOLT, Robert [CA/CA]; 1601 Appin Road, North Vancouver, British Columbia V7J 2T7 (CA). UPTON, Christopher [CA/CA]; 4427 Emily Carr Drive, Victoria, British Columbia V8X 4M2 (CA). ROPER, Rachel [US/US]; 754 Gatewood Drive, Winterville, NC 28590 (US). ASTELL, Caroline [CA/CA]; 4832 Blenheim Street, Vancouver, British Columbia V6L 3A7 (CA). JONES, Steven [GB/CA]; 1361 Wynbrook Place, Burnaby, British Columbia V5A 3Y6 (CA).

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[Continued on next page]

(54) Title: SARS VIRUS NUCLEOTIDE AND AMINO ACID SEQUENCES AND USES THEREOF

## Replicase 1A



(57) Abstract: The invention provides, in part, the genomic sequence of a putative coronavirus, the SARS virus, and provides novel nucleic acid and amino acid sequences that may be used, for example, for the diagnosis, prophylaxis, or therapy of a variety of SARS virus related disorders.

0 2004/096842 A3 IIII



GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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#### Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

### INTERNATIONAL SEARCH REPORT

Intermediate No PCT/CA2004/000626

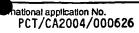
A. CLASSI IPC 7	ification of Subject matter C07K14/165 C12N15/11 A61K39/2	215					
According to	According to International Patent Classification (IPC) or to both national classification and IPC						
B. FIELDS	B. FIELDS SEARCHED						
Minimum do	ocumentation searched (classification system followed by classification	on symbols)					
IPC 7	CO7K C12N A61K						
Dogumento	tion searched other than minimum documentation to the extent that s	uch documents are included in the fields se	arched				
Cocumenta	ion searched directinal minimum cocumentation to the extent that s	acti accuments are included in the local se					
Electronic d	tata base consulted during the International search (name of data base	se and, where practical, search terms used)					
EPO-In	ternal, EMBASE, BIOSIS, WPI Data, PA	J					
	· ·						
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT						
Category •	Citation of document, with indication, where appropriate, of the rela	evant passages	Relevant to claim No.				
X	DATABASE GENBANK 'Online! 25 April 2003 (2003-04-25), "SARS coronavirus, complete genome" XP002294214		1-64				
	retrieved from NCBI						
	Database accession no. NC_004718 'gi:29826277!						
	abstract		·				
X	DATABASE GENBANK 'Online! 9 April 2003 (2003-04-09), "SARS coronavirus, complete genome" XP002294215		1-64				
	retrieved from NCBI		•				
	Database accession no. NC_004718 'gi:30124072!						
	abstract		•				
		·/					
		′					
X Furl	her documents are listed in the continuation of box C.	Patent family members are listed in	n annex.				
Special ca	alegories of cited documents:	"T" later document published after the inte	mational filing date				
	T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the						
'E' earlier	considered to be of particular relevance invention  earlier document but published on or after the international "X" document of particular relevance; the claimed invention						
"L" docume	filing date  cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone						
citatio	which is cited to establish the publication date of another citation or other special reason (as specified)  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the						
other	*O* document referring to an oral disclosure, use, exhibition or other means other means such combination being obvious to a person skilled in the art.						
*P' document published prior to the international filing date but later than the priority date claimed  *8' document member of the same patent family							
Date of the actual completion of the international search  Date of mailing of the international search report							
3	30 August 2004		<b>0</b> 1. 02. <b>05</b>				
Name and	mailing address of the ISA  European Patent Office, P.B. 5818 Patentlaan 2	Authorized officer					
	NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Petri, B					

## INTERNATIONAL SEARCH REPORT

Intermal Application No PCT/CA2004/000626

0.40	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	1	47 000020
Category *			Relevant to claim No.
	<u> </u>		
X	DATABASE GENBANK 'Online! 25 April 2003 (2003-04-25), "SARS coronavirus, complete genome" XP002294216 retrieved from NCBI		1-64
	Database accession no. NC_004718 'gi:30271926! abstract	·	
A	DATABASE GENBANK 'Online! 21 April 2003 (2003-04-21), "SARS coronavirus Urbani" XP002294217 retrieved from NCBI Database accession no. AY278741 'gi:30027617! abstract		
A	DATABASE GENBANK 'Online! 21 April 2003 (2003-04-21), "SARS coronavirus CUHK-W1" XP002294245 retrieved from NCBI Database accession no. AY278554 'gi:30027610! abstract		
Ρ,Χ	ROTA P A ET AL: "Characterization of a novel coronavirus associated with severe acute respiratory syndrome" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, US, vol. 300, no. 5624, 30 May 2003 (2003-05-30), pages 1394-1399, XP002269482 ISSN: 0036-8075 the whole document		1-64
Ρ,Χ	MARRA M A ET AL: "The Genome sequence of the SARS-associated coronavirus" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, US, vol. 300, no. 5624, 30 May 2003 (2003-05-30), pages 1399-1404, XP002276584 ISSN: 0036-8075 the whole document		1-64

## INTERNATIONAL SEARCH REPORT



Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: 65-66 because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 56-61 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. X Claims Nos.: 3 in part because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
see additional sheet
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. X No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the Invention first mentioned in the claims; it is covered by claims Nos.:
1-5; 6-64 (in part)
Remark on Protest The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

#### Continuation of Box II.1

Although claims 55-61 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: 65-66

The subject-matter of claims 65 and 66 relate only to the presentation of structural information and is not regarded as an patentable invention within the meaning of Rule 39.1(v) PCT. This information is disclosed as nucleic acid / amino acid sequences and stored in the form of computer readable records.

Continuation of Box II.2

Claims Nos.: 3 in part

The Sequence Listing as originally filed does not comprise Seq. Id. No. desigantors 208, 209. Reference to these Seq.Id.Nos is unclear.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.